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AMIDE-SUBSTITUTED 1,2,4-TRIAZIN-5(2H)-ONES FOR THE TREATMENT OF CHRONIC INFLAMMATORY DISEASES

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The invention relates to amide-substituted 1,2,4-triazin-5(2H)-ones and to processes for preparing them and also to their use for preparing medicaments for the treatment and/or prophylaxis of diseases, particularly of chronic inflammatory disorders, such as rheumatoid disorders, and cardiovascular disorders, such as dyslipidaemias, arteriosclerosis and coronary cardiac disorders, for example.

The synthesis of amide-substituted 1,2,4-triazin-5(2H)-ones is described in G. Hornyak, et al., *Acta Chimica Academiae Scientiarum Hungaricae*, **1969**, *61(2)*, 181-196.

WO 03/41712 relates inter alia to triazinones as Lp-PLA2 inhibitors for treating arteriosclerosis.

The inflammatory component in the pathophysiology of arteriosclerosis is nowadays generally acknowledged. The inflammatory vascular changes come about through the reaction of inwardly migrating monocytes with pathogenic lipoproteins in the arterial wall. The development of foam cells from the monocytes that have migrated in, by absorption of oxidized lipids, is central to the development and stability of plaque. In order to be recognized by monocytes, native lipoproteins must be modified to an atherogenic form. The enzyme platelet-activating factor acetylhydrolase (PAF-AH) is critically involved in this process, by forming, from oxidized LDL (low-density lipoprotein), the inflammation mediators lysophosphatidylcholine and also oxidized fatty acids.

Plasma PAF-AH is a calcium-independent member of the phospholipase A2 family that is secreted by monocytes and macrophages. The substrates of PAF-AH are platelet-activating factor (PAF) and oxidized phospholipids in oxidized LDL (oxLDL). Elimination of an acyl radical in position sn-2 produces oxidized fatty acids and lysophosphatidylcholine (lysoPC). The proinflammatory mediator lysoPC is responsible for the accumulation of cholesterol esters of loaded monocytes (foam cells) in the arteries (Quinn, et al., *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 2805-2809). This leads to the development of what are called 'fatty streaks', which represents the first visible arteriosclerotic vascular change. An inhibitor of PAF-AH would halt the formation of these macrophage-enriched lesions and would therefore be useful for the treatment of arteriosclerosis.

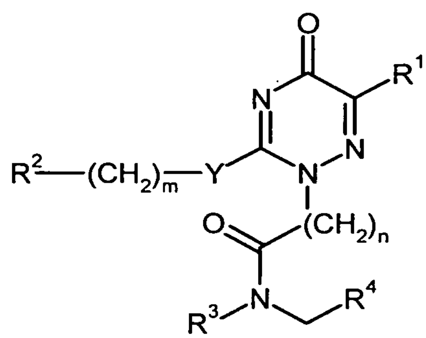
The increased lysoPC content of oxLDL also appears to be responsible for the endothelial dysfunction observed in patients with arteriosclerosis. Consequently PAF-AH inhibitors are also suitable for the treatment of this phenomenon. Their use would also be well advised in all disorders with an underlying endothelial dysfunction, such as diabetes, hypertension and angina pectoris, for example.

PAF-AH inhibitors could, moreover, find application in any disease exhibiting activated monocytes, macrophages or lymphocytes, since all of these cells express the enzyme.

It is an object of the present invention, therefore, to provide new inhibitors of PAF-AH for treating chronic inflammatory disorders and cardiovascular disorders in humans and animals.

Surprisingly, it has been found that the amide-substituted 1,2,4-triazin-5(2H)-ones described in the present invention are inhibitors of PAF-AH.

The invention provides compounds of the formula



(I)

in which

Y is an oxygen atom or a sulphur atom,

m is a number 1, 2 or 3,

n is a number 1, 2, 3 or 4,

R^1 is C_1-C_6-alkyl or C_3-C_7-cycloalkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, oxo, phenyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^2 is 5- to 10-membered heteroaryl,

it being possible for heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, aryl, aryloxy, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

R^3 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, alkoxy, alkylamino, hydroxyalkylamino, alkylthio, heterocyclyl, heteroaryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

in which heterocyclyl and heteroaryl can in turn be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

or

R^3 is a 3- to 8-membered heterocyclyl having 1 or 2 nitrogen atoms,

it being possible for heterocyclyl to be substituted by 1 or 2 substituents selected independently of one another from the group consisting of optionally hydroxyl-, amino- or alkoxy-substituted alkyl,

R^4 is aryl or heteroaryl,

it being possible for aryl and heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, alkylsulphonyl, aryl, aryloxy, heteroaryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, alkylaminosulphonyl and alkylsulphonylamino,

in which alkyl, alkoxy, alkylthio and alkylsulphonyl can be substituted by from 1 to 3 halogen substituents,

and

in which aryl and heteroaryl can in turn be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, alkylsulphonyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, alkylaminosulphonyl and alkylsulphonylamino,

in which alkyl, alkoxy, alkylthio and alkylsulphonyl can in turn be substituted by from 1 to 3 halogen substituents,

and their salts, their solvates and the solvates of their salts.

Compounds of the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, and also the compounds encompassed by formula (I) and mentioned below as exemplary embodiment(s), and their salts, solvates and solvates of the salts, provided that the compounds encompassed by formula (I) and mentioned below are not already salts, solvates or solvates of the salts.

Depending on their structure, the compounds of the invention may exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore provides the enantiomers or diastereomers and their respective mixtures. From such mixtures of enantiomers and/or diastereomers it is possible in a known way to isolate the stereoisomerically pure constituents.

Where the compounds of the invention can occur in tautomeric forms, the present invention encompasses all of the tautomeric forms.

Preferred salts for the purposes of the present invention are physiologically acceptable salts of the compounds of the invention. Also encompassed, however, are salts which, while not themselves being suitable for pharmaceutical applications, can be used, for example, for isolating or purifying the compounds of the invention.

Physiologically acceptable salts of the compounds of the invention encompass acid addition salts of mineral acids, carboxylic acids and sulphonic acids, such as salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds of the invention also encompass salts of customary bases, such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or from organic amines having 1 to 16 carbon atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, ethylenediamine and *N*-methylpiperidine.

Solvates for the purposes of the invention are those forms of the compounds of the invention that form a complex in the solid or liquid state through coordination with solvent molecules. Hydrates are one specific form of solvates, where the coordination takes place with water.

The free base of the salts of the compounds of the invention can be obtained, for example, by adding an aqueous base, dilute sodium hydroxide solution, for example, followed by extraction with a solvent by methods known to the person skilled in the art.

In the context of the present invention the substituents, unless specified otherwise, have the following definition:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylthio, alkylamino, alkylsulphonyl, alkoxycarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, alkylaminosulphonyl and alkylsulphonylamino are a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4, more preferably 1 to 3 carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy is by way of example and preferably methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylthio is by way of example and preferably methylthio, ethylthio, n-propylthio, isopropylthio, tert-butylthio, n-pentylthio and n-hexylthio.

Alkylamino is an alkylamino radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-tert-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

C_1-C_3-Alkylamino is for example a monoalkylamino radical having 1 to 3 carbon atoms or a dialkylamino radical having 1 to 3 carbon atoms per alkyl substituent.

Alkylsulphonyl is by way of example and preferably methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl and n-hexylsulphonyl.

Alkoxycarbonyl is by way of example and preferably methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Alkylaminocarbonyl is an alkylaminocarbonyl radical having one or two alkyl substituents (chosen independently of one another), the alkyl substituents independently of one another having generally 1 to 6, preferably 1 to 4, more preferably 1 to 3 carbon atoms, by way of example and preferably

methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-Diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-tert-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

C_1-C_3-Alkylaminocarbonyl is for example a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or a dialkylaminocarbonyl radical having 1 to 3 carbon atoms per alkyl substituent.

Alkylcarbonyl is by way of example and preferably methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl and n-hexylcarbonyl.

Alkylcarbonylamino is by way of example and preferably methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino, n-pentylcarbonylamino and n-hexylcarbonylamino.

Alkylaminosulphonyl is an alkylaminosulphonyl radical having one or two alkyl substituents (chosen independently of one another), the alkyl substituents independently of one another generally having 1 to 6, preferably 1 to 4, more preferably 1 to 3 carbon atoms, by way of example and preferably methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, isopropylaminosulphonyl, tert-butylaminosulphonyl, n-pentylaminosulphonyl, n-hexylaminosulphonyl, *N,N*-dimethylaminosulphonyl, *N,N*-diethylaminosulphonyl, *N*-ethyl-*N*-methylaminosulphonyl, *N*-methyl-*N*-n-propylaminosulphonyl, *N*-isopropyl-*N*-n-propylaminosulphonyl, *N*-tert-butyl-*N*-methylaminosulphonyl, *N*-ethyl-*N*-n-pentylaminosulphonyl and *N*-n-hexyl-*N*-methylaminosulphonyl.

C_1-C_3-Alkylaminosulphonyl is for example a monoalkylaminosulphonyl radical having 1 to 3 carbon atoms or a dialkylaminosulphonyl radical having 1 to 3 carbon atoms per alkyl substituent.

Alkylsulphonylamino is by way of example and preferably methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, tert-butylsulphonylamino, n-pentylsulphonylamino and n-hexylsulphonylamino.

Cycloalkyl is a cycloalkyl group having generally 3 to 8, preferably 5 to 7 carbon atoms; mentioned by way of example and preferably for cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Aryl is a mono- to tricyclic aromatic radical having generally 6 to 14, preferably 6 to 10 carbon atoms; mentioned by way of example and preferably for aryl are phenyl, naphthyl and phenanthrenyl.

Aryloxy is a mono- to tricyclic aromatic radical having generally 6 to 14, preferably 6 to 10 carbon atoms which is attached via an oxygen atom; mentioned by way of example and preferably for aryloxy are phenoxy, naphthyloxy and phenanthrenyloxy.

Heteroaryl is an aromatic, mono- or bicyclic radical having generally 5 to 10, preferably 5 or 6 ring atoms and up to 5, preferably up to 4, heteroatoms from the series S, O and N, it being possible for a nitrgoen atom also to form an N-oxide, by way of example and preferably thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzimidazolyl.

Heterocyclyl is a mono- or bicyclic, heterocyclic radical having generally 4 to 10, preferably 5 to 8 ring atoms and up to 3, preferably up to 2, heteroatoms and/or heterogroups from the series N, O, S, SO, SO_2, it being possible for a nitrogen atom also to form an N-oxide. The heterocyclyl radicals may be saturated or partially unsaturated. Preference is given to 5- to 8-membered, monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the series O, N and S, by way of example and preferably oxetan-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, tetrahydrofuranyl, tetrahydrothienyl, pyranyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, thiopyranyl, morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, perhydroazepinyl, piperazin-1-yl, piperazin-2-yl.

Halogen is fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine.

A symbol * on a bond indicates the linkage point in the molecule.

If radicals in the compounds of the invention are substituted, the radicals, unless specified otherwise, can be substituted singly or multiply, identically or differently. Substitution with up to three identical or different substituents is preferred. Very particular preference is given to substitution by one substituent.

Preferred compounds of the formula (I) are those in which

Y is an oxygen atom or a sulphur atom,

m is a number 1 or 2,

n is a number 1, 2 or 3,

R^1 is C_1-C_6-alkyl or C_3-C_6-cycloalkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, oxo, phenyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^2 is 5- to 10-membered heteroaryl,

it being possible for heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, aryl, aryloxy, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

R^3 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, alkoxy, alkylamino and hydroxyalkylamino,

or

R^3 is a 5- to 7-membered heterocyclyl having 1 or 2 nitrogen atoms,

it being possible for heterocyclyl to be substituted by 1 or 2 substituents selected independently of one another from the group consisting of optionally hydroxyl-, amino- or alkoxy-substituted alkyl,

R^4 is aryl or heteroaryl,

it being possible for aryl and heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, aryl, aryloxy, heteroaryl, alkylaminocarbonyl and alkylcarbonylamino,

in which alkyl and alkoxy can be substituted by from 1 to 3 halogen substituents,

and

in which aryl and heteroaryl can in turn be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylaminocarbonyl and alkylcarbonylamino,

in which alkyl and alkoxy can in turn be substituted by from 1 to 3 halogen substituents,

and their salts, their solvates and the solvates of their salts.

Further preferred compounds of the formula (I) are those in which

Y is a sulphur atom,

m is the number 1,

n is the number 1,

R^1 is C_1-C_4-alkyl, cyclopentyl or cyclohexyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of fluorine, cyano, oxo, phenyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^2 is pyridyl, thienyl, furyl, thiazolyl, oxadiazolyl, benzimidazolyl or benzoxazolyl,

it being possible for pyridyl, thienyl, furyl, thiazolyl, oxadiazolyl, benzimidazolyl and benzoxazolyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, trifluoromethyl, trifluoromethoxy and methyl,

R^3 is hydrogen or C_1-C_4-alkyl,

it being possible for alkyl to be substituted by one substituent selected from the group consisting of amino and C_1-C_4-alkylamino,

or

R^3 is piperidinyl or pyrrolidinyl,

it being possible for piperidinyl and pyrrolidinyl to be substituted by one C_1-C_4-alkyl substituent,

R^4 is phenyl,

it being possible for phenyl to be substituted by one substituent selected from the group consisting of trifluoromethyl, trifluoromethoxy, C_1-C_4-alkyl, C_1-C_4-alkoxy and phenyl,

in which phenyl can in turn be substituted by one substituent selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, C_1-C_3-alkyl and C_1-C_3-alkoxy,

and their salts, their solvates and the solvates of their salts.

Further preferred compounds of the formula (I) are those in which

Y is a sulphur atom,

m is the number 1,

n is the number 1,

R^1 is C_1-C_4-alkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of fluorine, cyano, oxo, phenyl and alkoxycarbonyl,

R^2 is pyridyl, thienyl, furyl or thiazolyl,

it being possible for pyridyl, thienyl, furyl and thiazolyl to be substituted by from 1 to 3 substituents selected independently from one another from the group consisting of halogen, trifluoromethyl, trifluoromethoxy and methyl,

R^3 is hydrogen or C_1-C_4-alkyl,

it being possible for alkyl to be substituted by one substituent selected from the group consisting of amino and C_1-C_4-alkylamino,

or

R^3 is piperidinyl or pyrrolidinyl,

it being possible for piperidinyl and pyrrolidinyl to be substituted by one C_1-C_4-alkyl substituent,

R^4 is phenyl,

it being possible for phenyl to be substituted by one substituent selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and phenyl,

in which phenyl can in turn be substituted by one substituent selected from the group consisting of halogen, trifluoromethyl, C_1-C_3-alkyl and C_1-C_3-alkoxy,

and their salts, their solvates and the solvates of their salts.

Further preferred compounds of the formula (I) are those in which

Y is an oxygen atom or a sulphur atom,

m is a number 1, 2 or 3,

n is a number 1, 2, 3 or 4,

R^1 is C_1-C_6-alkyl or C_3-C_7-cycloalkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, oxo, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^2 is 5- to 10-membered heteroaryl,

it being possible for heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, aryl, aryloxy, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

R^3 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, alkoxy, alkylamino, hydroxyalkylamino, alkylthio, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

R^4 is aryl or heteroaryl,

it being possible for aryl and heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, alkylsulphonyl, aryl, aryloxy, heteroaryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, alkylaminosulphonyl and alkylsulphonylamino,

in which aryl and heteroaryl can in turn be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, alkylsulphonyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, alkylaminosulphonyl and alkylsulphonylamino,

and their salts, their solvates and the solvates of their salts.

Preferred compounds of the formula (I) are those in which

Y is an oxygen atom or a sulphur atom,

m is a number 1 or 2,

n is a number 1, 2 or 3,

R^1 is C_1-C_6-alkyl or C_3-C_6-cycloalkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, oxo, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^2 is 5- to 10-membered heteroaryl,

it being possible for heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylthio, aryl, aryloxy, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl and alkylcarbonylamino,

R^3 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of hydroxyl, amino, alkoxy, alkylamino and hydroxyalkylamino,

R^4 is aryl or heteroaryl,

it being possible for aryl and heteroaryl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, aryl, aryloxy, heteroaryl, alkylaminocarbonyl and alkylcarbonylamino,

in which aryl and heteroaryl can in turn be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, alkylamino, alkylaminocarbonyl and alkylcarbonylamino,

and their salts, their solvates and the solvates of their salts.

Further preferred compounds of the formula (I) are those in which

Y is a sulphur atom,

m is the number 1,

n is the number 1,

R^1 is C_1-C_4-alkyl or cyclohexyl,

it being possible for alkyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of fluorine, oxo and alkoxycarbonyl,

R^2 is pyridyl, thienyl, furyl or benzoxazolyl,

it being possible for pyridyl, thienyl, furyl and benzoxazolyl to be substituted by from 1 to 3 substituents selected independently of one another from the group consisting of halogen, trifluoromethyl and trifluoromethoxy,

R^3 is hydrogen or diethylaminoethyl,

R^4 is phenyl,

it being possible for phenyl to be substituted by one phenyl,

in which phenyl can in turn be substituted by one substituent selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, C_1-C_3-alkyl and C_1-C_3-alkoxy,

and their salts, their solvates and the solvates of their salts.

Further preferred compounds of the formula (I) are those in which Y is a sulphur atom.

Further preferred compounds of the formula (I) are those in which m is the number 1.

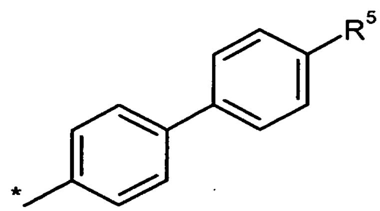
Further preferred compounds of the formula (I) are those in which n is the number 1.

Further preferred compounds of the formula (I) are those in which R^1 is ethyl, ethoxycarbonylethyl, 3-oxobut-1-yl, trifluoromethyl or cyclohexyl.

Further preferred compounds of the formula (I) are those in which R^2 is pyridyl, thienyl, furyl or benzoxazolyl.

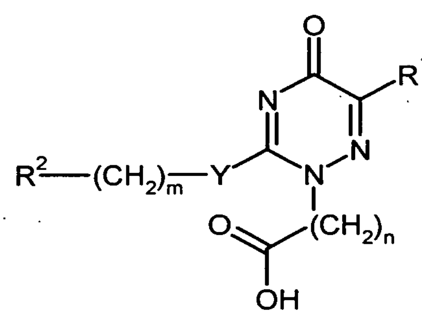
Further preferred compounds of the formula (I) are those in which R^3 is hydrogen or diethylaminoethyl.

Further preferred compounds of the formula (I) are those in which R^4 is a substituent of the formula



where R^5 is hydrogen, halogen, trifluoromethyl or trifluoromethoxy.

The invention further provides a process for preparing the compounds of the formula (I), where compounds of the formula

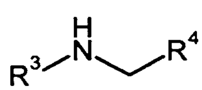


(II)

in which

Y, m, n, R^1 and R^2 are as defined above are reacted

with compounds of the formula



(III)

in which

R^3 and R^4 are as defined above.

The reaction takes place generally in inert solvents, in the presence of dehydrating reagents, optionally in the presence of a base, preferably in a temperature range from 0°C to room temperature under atmospheric pressure.

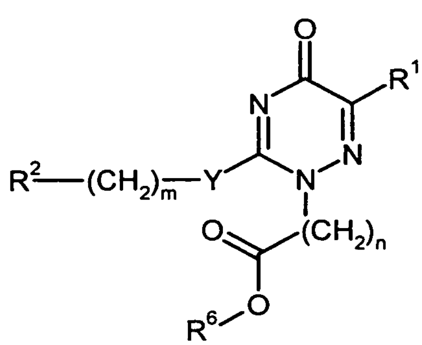
Examples of suitable dehydrating reagents in this context are carbodiimides such as *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide, *N*-(3-dimethylaminoisopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) (optionally in the presence of pentafluorophenol (PFP)), *N*-cyclohexylcarbodiimide-*N'*-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride or benzotriazolyloxy-tri(dimethylamino)phosphonium hexafluorophosphate, or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP), or mixtures of these, with bases. Preferably the condensation is carried out with HOBt and EDC.

Bases are, for example, alkali metal carbonates, such as sodium or potassium carbonate, or hydrogen carbonate, or organic bases such as trialkylamines, such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine. Preferably the condensation is carried out with diisopropylethylamine.

Inert solvents are for example halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbons such as benzene, nitromethane, dioxane, dimethylformamide, acetonitrile or hexamethylphosphoramide. It is also possible to use mixtures of the solvents. Particular preference is given to dichloromethane or dimethylformamide.

The compounds of the formula (III) are known or can be synthesized by known methods from the corresponding reactants.

The compounds of the formula (II) are known or can be prepared by reacting compounds of the formula



(III)

in which

Y, m, n, R^1 and R^2 are as defined above and

R^6 is alkyl, preferably methyl, ethyl or tert-butyl,

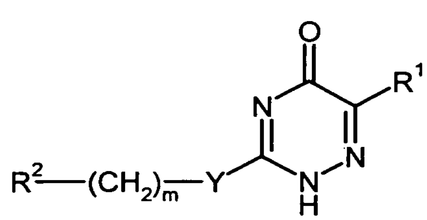
with bases (methyl, ethyl) or with acids (tert-butyl).

The reaction takes place in general in inert solvents, preferably in a temperature range from 0°C to room temperature under atmospheric pressure.

In the case of the reaction with bases, examples of suitable bases include alkali metal hydroxides such as sodium, lithium or potassium hydroxide, or alkali metal carbonates such as caesium carbonate, sodium or potassium carbonate, sodium hydroxide being preferred. Examples of solvents are halogenated hydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane or tetrahydrofuran, alcohols such as methanol, ethanol, n-propanol or isopropanol, or other solvents such as dimethylformamide, dimethylacetamide, dimethyl sulphoxide, acetonitrile or pyridine, or mixtures of solvents; preferred solvents are tetrahydrofuran and/or methanol or dioxane.

In the case of the reaction with acids, examples of suitable acids include hydrogen chloride or trifluoroacetic acid. Examples of solvents are halogenated hydrocarbons such as dichloromethane or trichloromethane, or ethers such as diethyl ether, tetrahydrofuran or dioxane, or other solvents such as dimethylformamide or acetonitrile. It is also possible to use mixtures of the solvents. Particular preference is given to using hydrogen chloride in dioxane or trifluoroacetic acid in dichloromethane.

The compounds of the formula (III) are known or can be prepared by reacting compounds of the formula

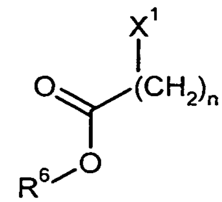


(IV)

in which

Y, m, R^1 and R^2 are as defined above,

with compounds of the formula



(V)

in which

n and R^6 are as defined above and

X^1 is halogen, preferably iodine or bromine.

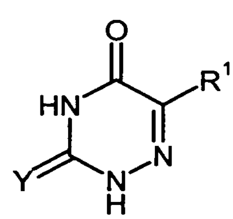
The reaction takes place in general in inert solvents, in the presence of a base, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Inert solvents are for example halogenated hydrocarbons such as methylene chloride, trichloromethane or 1,2-dichloroethane, ethers such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, or other solvents such as acetone, dimethylformamide, dimethylacetamide, 2-butanone or acetonitrile, preference being given to tetrahydrofuran or methylene chloride.

Bases are for example alkali metal carbonates such as caesium carbonate, sodium or potassium carbonate, or sodium or potassium methoxide, or sodium or potassium ethoxide or potassium tert-butoxide, or amides such as sodium amide, lithium bis-(trimethylsilyl)amide or lithium diisopropylamide, or other bases such as sodium hydride, DBU, triethylamine or diisopropylethylamine, preference being given to diisopropylethylamine.

The compounds of the formula (V) are known or can be synthesized by known methods from the corresponding reactants.

The compounds of the formula (IV) are known or can be prepared by reacting compounds of the formula



(VI)

in which

Y and R^1 are as defined above,

with compounds of the formula

$$R^2—(CH_2)_m—X^2 \qquad (VII)$$

in which

m and R^2 are as defined above and

X^2 is halogen, preferably iodine or bromine.

The reaction takes place in general in a solvent, in the presence of a base, preferably in a temperature range from 0°C to 40°C under atmospheric pressure.

Solvents are for example halogenated hydrocarbons such as methylene chloride, trichloromethane or 1,2-dichloroethane, ethers such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, or other solvents such as acetone, dimethylformamide, dimethylacetamide, 2-butanone or acetonitrile, or water or mixtures of the solvents with water, water being preferred.

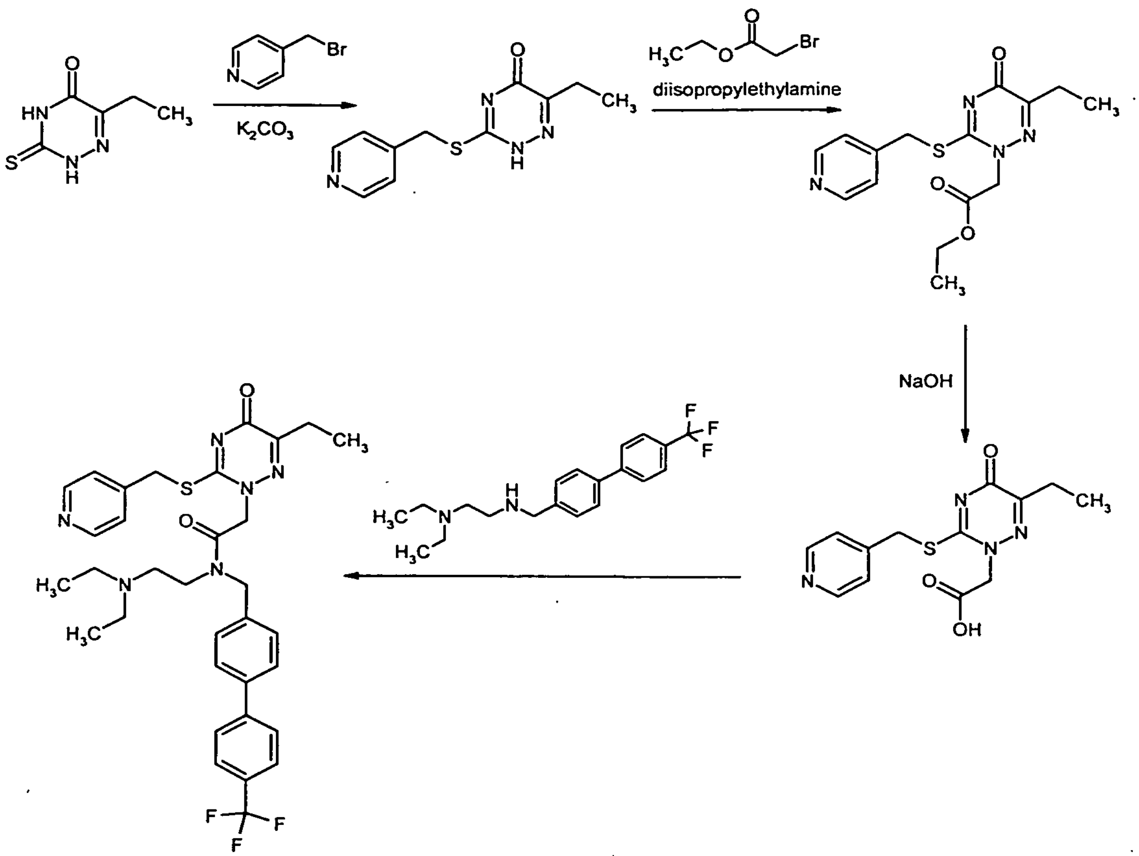
Bases are for example alkali metal carbonates such as caesium carbonate, sodium or potassium carbonate, or sodium or potassium methoxide, or sodium or potassium ethoxide or potassium tert-butoxide, or amides such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropyl-amide, or other bases, such as sodium hydride, DBU, triethylamine or diisopropylethylamine, potassium carbonate being preferred.

One equivalent of the compounds of the formula (VII) is used, based on the compounds of the formula (VI).

The compounds of the formulae (VI) and (VII) are known or can be synthesized by known methods from the corresponding reactants.

The preparation of the compounds of the invention can be illustrated by the following synthesis scheme.

Scheme 1:



The compounds of the invention exhibit an unforeseeable and valuable spectrum of pharmacological activity.

They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and animals.

The pharmaceutical activity of the compounds of the invention can be explained by their action as PAF-AH inhibitors.

The present invention further provides for the use of the compounds of the invention for the treatment and/or prophylaxis of disorders, preferably of cardiovascular disorders, in particular of arteriosclerosis.

The compounds of the invention can be used in preventing and treating cardiovascular disorders, such as arteriosclerosis, reperfusion tissue damage after stroke, myocardial infarction or peripheral arterial and venous vascular disorders and essential or pregnancy-induced hypertension.

The compounds of the invention can further be used in any kind of disorders involving lipid oxidation, inflammation and increased enzyme activity, such as arthritis, rheumatoid arthritis,

diabetes mellitus, kidney inflammation, osteoporosis, Crohn's disease, chronic inflammatory lung diseases such as adult respiratory distress syndrome (ARDS), inflammatory disorders of the brain such as Alzheimer's disease, sepsis and acute and chronic inflammation, restenosis after PTCA, transplant rejections, chronic inflammatory fibrotic changes in organs, such as hepatic fibrosis, or the generalized autoimmune disease systemic lupus erythematosus or other forms of lupus erythematosus or dermal inflammatory diseases such as psoriasis.

On the basis of their pharmacological properties the compounds of the invention can be used alone and where necessary in combination with other active ingredients, in particular with antihyperlipidaemic, antiarteriosclerotic, antidiabetic, antiinflammatory or antihypertensive ingredients. Examples thereof are cholsterol synthesis inhibitors such as statins, antioxidants such as probucol, PPAR activators, insulin sensitizers, calcium channel antagonists, and non-steroidal antirheumatics.

The present invention further provides for the use of the compounds of the invention for the treatment and/or prophylaxis of disorders, particularly the abovementioned disorders.

The present invention further provides for the use of the compounds of the invention for preparing a medicament for the treatment and/or prophylaxis of disorders, particularly the abovementioned disorders.

The present invention further provides a method for the treatment and/or prophylaxis of disorders, particularly the abovementioned disorders, using a therapeutically effective amount of the compounds of the invention.

The compounds of the invention may act systemically and/or locally. For that purpose they can be administered in a suitable way, such as by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival, otic route, or as an implant or stent.

For these administration routes the compounds of the invention can be administered in suitable forms.

Administration forms suitable for oral administration are those forms which function in accordance with the prior art and deliver the compounds of the invention rapidly and/or in a modified way, and which comprise the compounds of the invention in crystalline and/or amorphized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets), for example with enteric coatings or coatings which are insoluble or dissolve with a delay and control the release of the compound of the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilizates, capsules (hard or soft gelatin capsules, for example), pan-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration may take place such as to avoid an absorption step (e.g. intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of absorption (e.g. intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration include injection preparations and infusion preparations in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Oral administration is preferred.

For the other administration routes suitable pharmaceutical forms are, for example, inhalation forms (including powder inhalers, nebulizers), nasal drops, solutions and sprays; tablets for lingual, sublingual or buccal administrations, films/wafers or capsules, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as patches, for example), milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted into the stated administration forms. This can be conventionally by mixing with inert, nontoxic, pharmaceutically suitable excipients. These excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecyl sulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as ascorbic acid, for example), colorants (e.g. inorganic pigments such as iron oxides, for example) and taste and/or odour corrigents.

The present invention further provides medicaments which comprise at least one compound of the invention, normally together with one or more inert, nontoxic, pharmaceutically suitable excipients, and also provides for their use for the aforementioned purposes.

In general it has proven to be advantageous in the case of parenteral administration to administer amounts of from about 5 to 250 mg/kg body weight per 24 hours in order to achieve effective results. In the case of oral administration the amount is approximately from 5 to 100 mg/kg body weight per 24 hours.

Nevertheless it may be necessary where appropriate to deviate from the stated amounts, in particular as a function of the body weight, administration route, individual response to the active ingredient, nature of the preparation and time or interval at or over which administration takes place. Thus in certain cases it may be sufficient to make do with less than the aforementioned minimum amount, while in other cases the upper limit stated has to be exceeded. Where larger

amounts are administered it may be advisable to divide them into a number of individual doses over the day.

The percentages in the tests and examples below are weight percentages unless otherwise specified; parts are parts by weight. Solvent ratios, dilution ratios and concentrations of liquid/liquid solutions are in each case based on the volume. The indication "w/v" denotes "weight/volume". Thus, for example, "10% w/v" denotes that 100 ml of solution or suspension contain 10 g of substance.

A) Examples

Abbreviations:

abs.	Absolute
Boc	tert-butoxycarbonyl
$CDCl_3$	Deuterochloroform
CO_2	carbon dioxide
DIEA	*N,N*-diisopropylethylamine
DMSO	dimethyl sulphoxide
EDC	*N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
eq.	Equivalent
ESI	electrospray ionization (in MS)
h	Hour
HOBt	1-hydroxy-1H-benzotriazole
HPLC	high-pressure, high-performance liquid chromatography
conc.	Concentrated
LC-MS	liquid chromatography-coupled mass spectroscopy
min.	Minutes
MS	mass spectroscopy
MW	molecular weight [g/mol]
NMR	nuclear magnetic resonance spectroscopy
R_f	retention index (for TLC)
RP-HPLC	reverse phase HPLC
RT	room temperature
R_t	retention time (for HPLC)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

HPLC and LC-MS methods:

Method 1 (LC-MS): Instrument: Micromass Quattro LCZ, with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l water + 1 ml 50% formic acid, eluent B: 1 l acetonitrile + 1 ml 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 2 (LC-MS): MS instrument: Micromass ZQ; HPLC instrument: HP 1100 series; UV DAD; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 ml 50% formic acid, eluent B: 1 l acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 3 (LC-MS): MS instrument: Micromass ZQ; HPLC instrument: Waters Alliance 2795; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 ml 50% formic acid, eluent B: 1 l acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 4 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; eluent A: 5 ml $HClO_4$/l water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 6.5 min 90%B; flow rate: 0.75 ml/min; oven: 30°C; UV detection: 210 nm.

Method 5 (LC-MS): Instrument: Micromass Quattro LCZ with HPLC Agilent series 1100; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 ml 50% formic acid, eluent B: 1 l acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/ 4.5 min 2 ml/min; oven: 50°C; UV detection: 208- 400 nm.

Method 6 (HPLC): Instrument: Hewlett Packard series 1050; column: Symmetry TM C18 3.9 mm x 150 mm; eluent A: water, eluent B: acetonitrile; gradient: 0.0 min 10%B → 0.6 min 10%B → 3.8 min 100%B → 5.0 min 100%B → 5.5 min 10%B; run time: 6.0 min; flow rate: 1.5 ml/min; injection volume: 10 µl; UV detection: 214 nm and 254 nm.

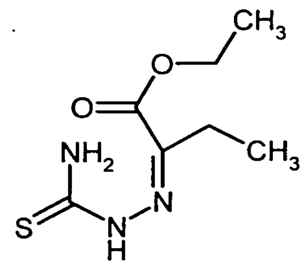
Method 7 (GC-MS): Instrument: Micromass GCT, GC6890; column: Restek RTX-35MS, 30 m x 250 µm x 0.25 µm; constant flow with helium: 0.88 ml/min; oven: 60°C; inlet: 250°C; gradient: 60°C (0.30 min hold), 50°C/min → 120°C, 16°C/min → 250°C, 30°C/min → 300°C (1.7 min hold).

Method 8 (preparative HPLC): column: GromSil C18, 250 mm x 30 mm; flow rate: 40 ml/min; run time: 40 min; detection: 210 nm; eluent A: water containing 0.05% formic acid, eluent B: acetonitrile, gradient: 5 min 10%B → 35 min 95%B → 37 min 95%B → 40.01 min 10%B.

Starting compounds:

Example 1A

Ethyl (2Z)-2-[(aminocarbonothioyl)hydrazono]butanoate



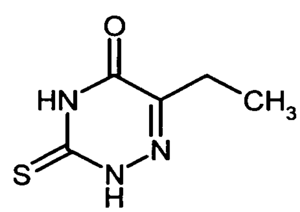
5.92 g (45.45 mmol) of ethyl 2-oxobutanate are dissolved in 30 ml of ethanol and 4.14 g (45.45 mmol) of thiosemicarbazide are added. Following addition of 0.23 ml of concentrated hydrochloric acid the reaction mixture is left stirring overnight at RT. The precipitate obtained is filtered off and washed with ethanol and the filtrate is concentrated. The solid which precipitates is isolated by filtration. In this way a total of 9.71 g (quant.) of crude product, which is not purified further, are obtained.

LC-MS (method 1): R_t = 2.08 min and 2.56 min (isomeric products)

MS (ES^+): m/z = 203 $(M)^+$

Example 2A

6-Ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one



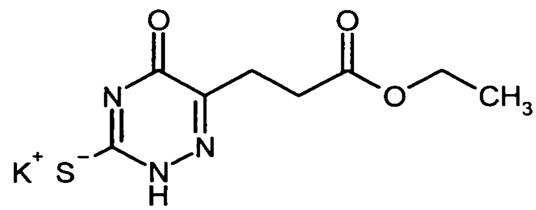
2.05 g (10.1 mmol) of ethyl 2-[2-(aminocarbonothioyl)hydrazino]butanate are suspended in 11 ml of ethanol. 1.13 g (20.2 mmol) of potassium hydroxide in solution in 11 ml of water are added. The mixture is stirred under reflux for 2 hours, then concentrated on a rotary evaporator and acidified with a few drops of concentrated hydrochloric acid. It is then cooled in an ice bath and the solid obtained is isolated by filtration. This gives 1.75 g (quant.) of crude product, which is not purified further.

HPLC (method 4): R_t = 2.04 min

MS (EI): m/z = 157 $(M)^+$

Example 3A

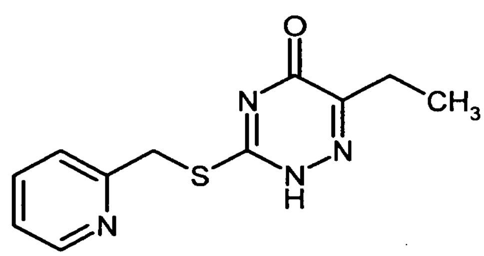
Potassium 6-(3-ethoxy-3-oxopropyl)-5-oxo-2,5-dihydro-1,2,4-triazine-3-thiolate



5 g (24.7 mmol) of diethyl 2-oxoglutarate are dissolved in 13 ml of ethanol, 2.25 g (24.7 mmol) of thiosemicarbazide and 0.12 ml of concentrated hydrochloric acid are added and the mixture is stirred at RT overnight. The precipitate is filtered off, washed with ethanol and dried in vacuo. The solid obtained is suspended in 25 ml of ethanol, 1.03 g of potassium hydroxide in solution in 25 ml of ethanol are added and the mixture is heated at reflux for 2 hours with stirring. Thereafter some of the solvent is evaporated. Icebath cooling causes a solid to precipitate which is filtered off and, after washing with diethyl ether, is dried in vacuo. This gives 5.55 g (79% of theory) of crude product, which is not purified further.

Example 4A

6-Ethyl-3-[(pyridin-2-ylmethyl)thio]-1,2,4-triazin-5(2H)-one



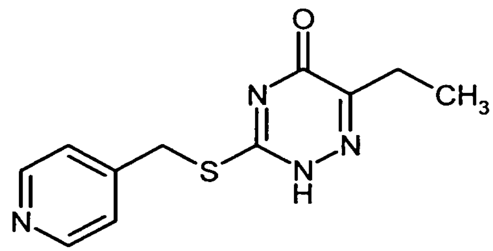
A solution of 100 mg (0.64 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 175.8 mg (1.27 mmol) of potassium carbonate in 10 ml of water is admixed with 162.5 mg (0.64 mmol) of 2-(bromomethyl)pyridine hydrobromide. After 14 h at room temperature the reaction solution is adjusted to a pH of 1 using 1 N hydrochloric acid and the reaction solution is purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 99 mg (44% of theory) of the title compound, which is reacted further without additional purification.

HPLC (method 4): R_t = 2.83 min.

MS (EI): m/z = 249 (M+H)$^+$.

Example 5A

6-Ethyl-3-[(pyridin-4-ylmethyl)thio]-1,2,4-triazin-5(2H)-one



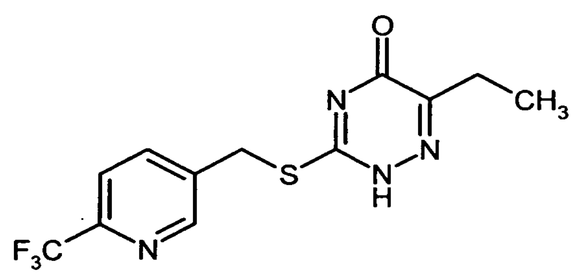
A solution of 100 mg (0.64 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 175.8 mg (1.27 mmol) of potassium carbonate in 10 ml of water is admixed with 162.5 mg (0.64 mmol) of 4-(bromomethyl)pyridine hydrobromide. After 14 h at room temperature the reaction solution is adjusted to a pH of 1 using 1N hydrochloric acid and purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 73 mg (44% of theory) of the title compound.

HPLC (method 4): R_t = 2.67 min.

MS (EI): m/z = 249 (M+H)$^+$.

Example 6A

6-Ethyl-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-5(2H)-one



x HCl

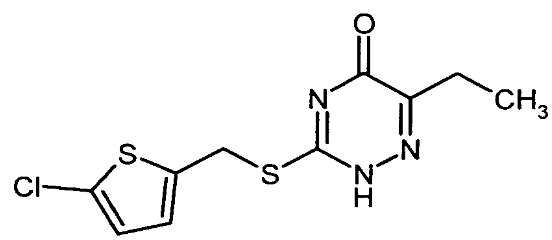
A solution of 160 mg (1.02 mmol) 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 140.7 mg (1.02 mmol) of potassium carbonate in 15 ml of water is admixed with 246.8 mg (1.03 mmol) of 5-(bromomethyl)-2-(trifluoromethyl)pyridine. After 14 h at room temperature the reaction mixture is adjusted to a pH of 1 using 1 ml 1 N hydrochloric acid and the precipitate formed is filtered off with suction, washed with water and dried under a high vacuum. This gives 213 mg (66% of theory) of the title compound.

HPLC (method 4): $R_t = 3.75$ min.

MS (EI): m/z = 317 $(M+H)^+$.

Example 7A

3-{[(5-Chloro-2-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one



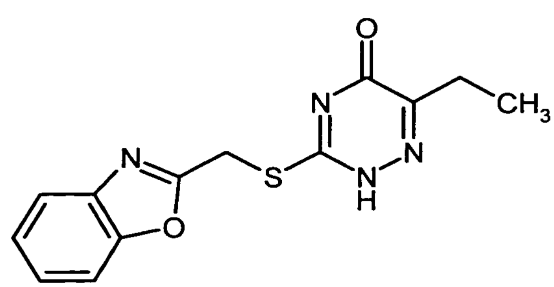
A solution of 160 mg (1.02 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 140.7 mg (1.02 mmol) of potassium carbonate in 15 ml of water is admixed with 171.7 mg (1.03 mmol) of 2-chloro-5-(chloromethyl)thiophene. After 14 h at room temperature the precipitate formed is isolated and the mother liquor is adjusted to a pH of 1 using 1 N hydrochloric acid. The precipitate formed is filtered off with suction, washed with water and dried under a high vacuum. Combining the solids gives 69.1 mg (21% of theory) of the title compound.

HPLC (method 4): $R_t = 4.05$ min.

MS (EI): m/z = 288 $(M+H)^+$.

Example 8A

3-[(1,3-Benzoxazol-2-ylmethyl)thio]-6-ethyl-1,2,4-triazin-5(2H)-one



A solution of 200 mg (1.27 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 175.8 mg (1.27 mmol) of potassium carbonate in 15 ml of water is admixed with 215.4 mg (1.29 mmol) of 2-(chloromethyl)-1,3-benzoxazole. After 18 h at room temperature the reaction mixture is extracted with dichloromethane. The aqueous phase is adjusted to a pH of 1 using 2 N hydrochloric acid and extracted three times with dichloromethane. The combined organic phaases

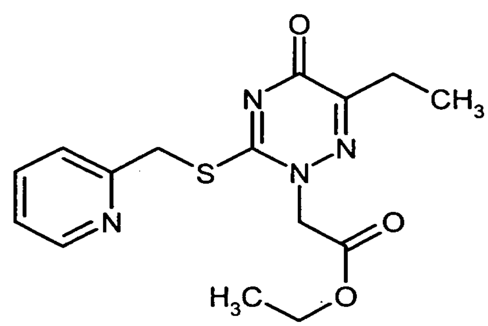
are dried over sodium sulphate, concentrated in vacuo and dried under a high vacuum. This gives 187 mg (46% of theory) of the title compound.

HPLC (method 4): $R_t = 3.61$ min.

MS (EI): m/z = 289 $(M+H)^+$.

Example 9A

Ethyl [6-ethyl-5-oxo-3-[(pyridin-2-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetate



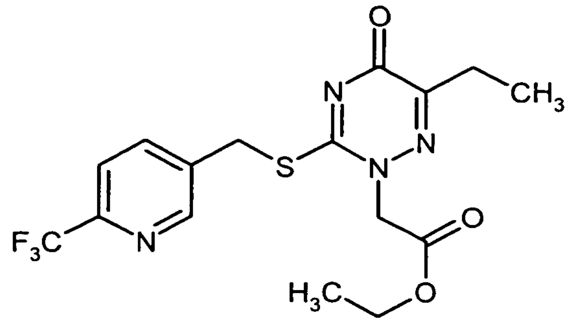
A solution of 79 mg (0.32 mmol) of 6-ethyl-3-[(pyridin-2-ylmethyl)thio]-1,2,4-triazin-5(2H)-one and 66.5 µl (0.38 mmol) of *N,N*-diisopropylamine in 1.0 ml of dichloromethane is admixed at 0°C with 39.5 µl (0.33 mmol) of ethyl iodoacetate. After 18 h at room temperature 3 ml of water are added to the reaction mixture. Following the evaporation of the dichloromethane on a rotary evaporator the remaining volume is purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 53 mg (50% of theory) of the title compound.

LC-MS (method 2): $R_t = 1.70$ min,

MS (ESI): m/z = 335 $(M+H)^+$.

Example 10A

Ethyl [6-ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-2(5H)-yl]acetate



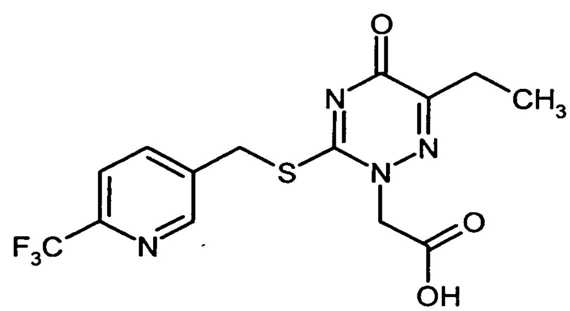
A solution of 104 mg (0.29 mmol) of 6-ethyl-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-5(2H)-one and 128.4 µl (0.74 mmol) of *N,N*-diisopropylamine in 1.0 ml of dichloromethane is admixed at 0°C with 36.6 µl (0.31 mmol) of ethyl iodoacetate. After 18 h at room temperature a further 36.6 µl (0.31 mmol) of ethyl iodoacetate are added and the mixture is stirred for a further 18 h. Following acidification with 1N hydrochloric acid the reaction mixture is purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 95 mg (77% of theory) of the title compound.

HPLC (method 4): $R_t = 4.35$ min.

MS (EI): m/z = 403 $(M+H)^+$.

Example 11A

[6-Ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-2(5H)-yl]acetic acid



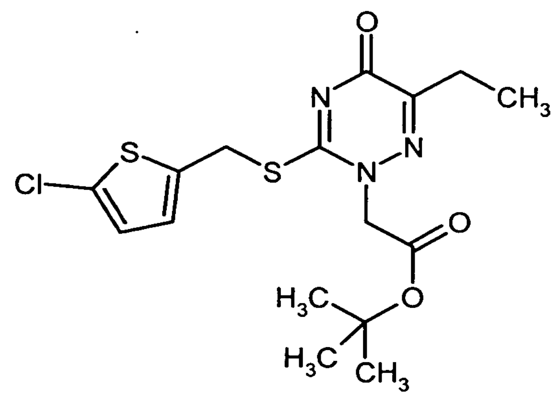
A solution of 40 mg (0.10 mmol) of ethyl [6-ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}-thio)-1,2,4-triazin-2(5H)-yl]acetate in 1.5 ml of dioxane is admixed at room temperature with 298 µl (0.15 mmol) of 1 N sodium hydroxide solution. After 35 minutes the reaction mixture is purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 19 mg (51% of theory) of the title compound.

LC-MS (method 3): $R_t = 1.46$ min,

MS (ESI): m/z = 375 $(M+H)^+$.

Example 12A

tert-Butyl [3-{[(5-chloro-2-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



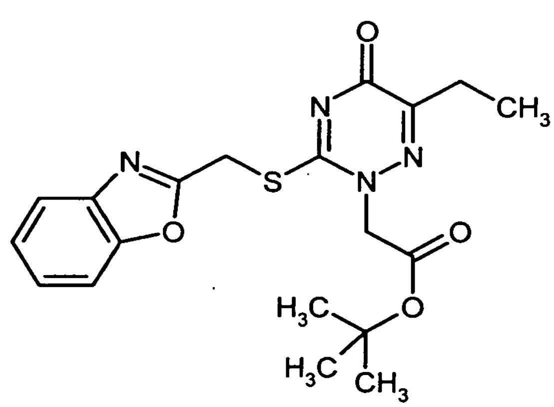
A solution of 50 mg (0.17 mmol) of 3-{[(5-chloro-2-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one and 36.3 µl (0.21 mmol) of *N,N*-diisopropylethylamine in 0.5 ml of dichloromethane is admixed at 0°C with 26.9 µl (0.18 mmol) of tert-butyl bromoactate. After 18 h at room temperature the reaction mixture is admixed with 3 ml of water and concentrated in vacuo to approximately 3 ml. The residue is purified by means of preparativer HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 49 mg (50% of theory) of the title compound, which is used further without additional purification.

LC-MS (method 2): R_t = 2.79 min,

MS (ESI): m/z = 402 $(M+H)^+$.

Example 13A

tert-Butyl [3-[(1,3-benzoxazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



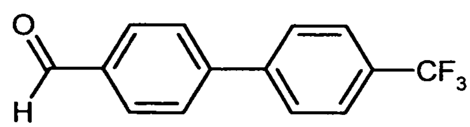
A solution of 100 mg (0.35 mmol) of 3-[(1,3-benzoxazol-2-ylmethyl)thio]-6-ethyl-1,2,4-triazin-5(2H)-one and 72.5 µl (0.42 mmol) of *N,N*-diisopropylethylamine in 1.0 ml of dichloromethane is admixed at 0°C with 53.8 µl (0.18 mmol) of tert-butyl bromoacetate. After 18 h at room temperature the reaction mixture is admixed with 3 ml of water and concentrated in vacuo to approximately 3 ml. The residue is purified by means of preparativer HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 104 mg (75% of theory) of the title compound.

HPLC (method 4): $R_t = 4.57$ min.

MS (EI): m/z = 403 $(M+H)^+$.

Example 14A

4'-(Trifluoromethyl)biphenyl-4-carbaldehyde



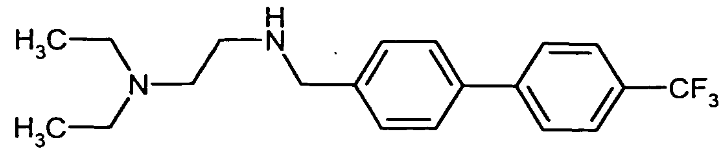
1.0 g (4.44 mmol) of 1-bromo-4-(trifluoromethyl)benzene, 1.13 g (7.56 mmol) of 4-formylphenyl-boronic acid and 0.94 g (8.89 mmol) of sodium carbonate are introduced as an initial charge in 7.5 ml of water and 20.0 ml of dimethoxyethane. Argon is passed through the mixture for 1 h. Then 0.26 g (0.22 mmol) of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) is added and the mixture is stirred at reflux for 18 h. The reaction mixture is taken up in 25 ml of ethyl acetate, filtered over kieselguhr, washed once each with 20 ml of 1 N hydrochloric acid and saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo. Following chromatography on silica gel (cyclohexane/ethyl acetate: 10/1 -> 3/1) the product fractions are concentrated and dried under a high vacuum. This gives 1.01 g (91% of theory) of the title compound.

HPLC (method 4): $R_t = 4.99$ min.

MS (EI): m/z = 285 $(M+N_2H_7)^+$.

Example 15A

N,N-Diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine



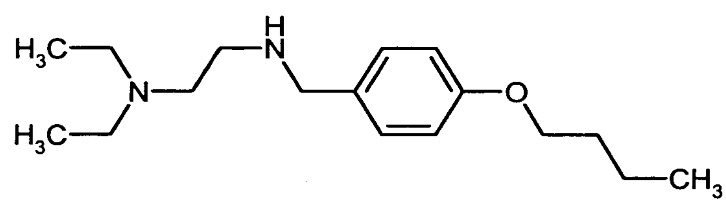
A solution of 500 mg (2.00 mmol) of 4'-(trifluoromethyl)biphenyl-4-carbaldehyde and 280.8 µl (2.00 mmol) of 1-amino-2-diethylaminoethane is admixed with 500 mg of 4 Å molecular sieve (powder, < 5 microns). After 18 h at room temperature the reaction mixture is filtered, washed with dichloromethane and concentrated in vacuo. The crude material is dissolved in 5 ml of abs. ethanol and admixed at 0°C with 90.7 mg (2.40 mmol) of sodium borohydride. After 1 h at room temperature the reaction mixture is admixed with water and extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated in vacuo. Following chromatography on silica gel (cyclohexane/ethyl acetate: 3/1) the product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 585 mg (75% of theory) of the title compound.

HPLC (method 4): $R_t = 4.10$ min.

MS (EI): m/z = 351 $(M+H)^+$.

Example 16A

N'-(4-Butoxybenzyl)-*N,N*-diethylethane-1,2-diamine



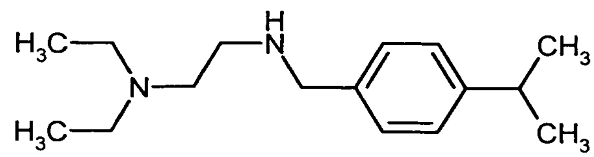
A solution of 2 g (11.2 mmol) of 4-butoxybenzaldehyde in 70 ml of dichloromethane is admixed with 1.58 ml (11.2 mmol) of 1-amino-2-diethylaminoethane and 3.5 g of 4 Å molecular sieve (powder, < 5 microns). After 18 h at room temperature the reaction mixture is filtered, washed with dichloromethane and concentrated in vacuo. The crude material is dissolved in 40 ml abs. ethanol and admixed at 0°C with 509 mg (13.5 mmol) of sodium borohydride. After 2 h at room temperature the reaction mixture is admixed with 50 ml of water and extracted with three times 100 ml of dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated in vacuo. Following chromatography on silica gel (cyclohexane/ethyl acetate: 1/1 ->3/1 -> toluene/ethanol/triethylamine 95/4/1) the product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 1.64 g (51% of theory) of the title compound.

HPLC (method 4): $R_t = 3.82$ min.

MS (EI): m/z = 279 $(M+H)^+$

Example 17A

N,N-Diethyl-*N'*-(4-isopropylbenzyl)ethane-1,2-diamine



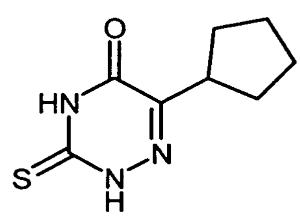
A solution of 2 g (13.5 mmol) of 4-isopropylbenzaldehyde in 70 ml of dichloromethane is admixed with 1.9 ml (13.5 mmol) of 1-amino-2-diethylaminoethane and 3.5 g of 4 Å molecular sieve (powder, < 5 microns). After 18 h at room temperature the reaction mixture is filtered, washed with dichloromethane and concentrated in vacuo. The crude material is dissolved in 40 ml of abs. ethanol and admixed at 0°C with 613 mg (16.2 mmol) of sodium borohydride. After 2 h at room temperature the reaction mixture is admixed with 50 ml of water and extracted with three times 100 ml of dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated in vacuo. Following chromatography on silica gel (cyclohexane/ethyl acetate: 1/1 -> 3/1 -> toluene/ethanol/triethylamine 95/4/1) the product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 2.07 g (60% of theory) of the title compound.

HPLC (method 4): $R_t = 3.65$ min.

MS (EI): m/z = 249 $(M+H)^+$

Example 18A

6-Cyclopentyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one



3.00 g (17.6 mmol) of ethyl 2-cyclopentyl-2-oxoacetate (preparable for example in accordance with Y. Akiyama et al., *Chem. Pharm. Bull.*, **1984**, *32 (5)*, 1800-1807) in 20 ml of ethanol are admixed with 1.61 g (17.6 mmol) of thiosemicarbazide and 88 µl of concentrated hydrochloric acid. The mixture is stirred at room temperature overnight. By adding 50 ml of water the reaction

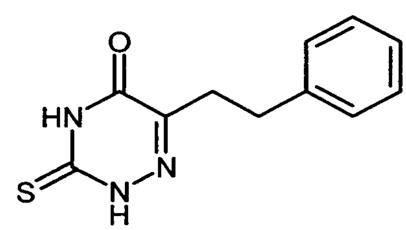
is ended. Following three-fold extraction with ethyl acetate (50 ml each time) the organic phases are dried over magnesium sulphate and freed from the solvent under reduced pressure. The residue is taken up in 11 ml of ethanol and 11 ml of water and admixed with 1.15 g (20.6 mmol) of potassium hydroxide. After heating under reflux for 2 h the mixture is adjusted to a pH of 1 using concentrated hydrochloric acid. The mixture is cooled and the precipitated solid is filtered off with suction. This gives 2.01 g of product (99% of theory).

MS (ESI): m/z = 198 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.52-1.74 (m, 6H), 1.75-1.96 (m, 2H), 3.04-3.23 (m, 1H), 12.96-13.27 (br. s, 2H).

Example 19A

6-(2-Phenylethyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one



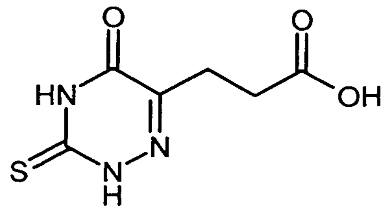
1.00 g (4.85 mmol) of ethyl benzylpyruvate in 6 ml of ethanol is admixed with 0.44 g (4.9 mmol) of thiosemicarbazide and 24 µl of concentrated hydrochloric acid. After the mixture has been stirred overnight at room temperature the precipitated solid is filtered off with suction. The mother liquor is freed from the solvent under reduced pressure. The residue and the isolated solid are taken up in 4 ml of water and 4 ml of ethanol. 402 mg (7.16 mmol) of potassium hydroxide are added and the mixture is heated under reflux for 2 h. The pH is adjusted to 1 using concentrated hydrochloric acid. The mixture is cooled and the precipitated solid is filtered off with suction. This gives 678 mg of product (81% of theory).

MS (ESI): m/z = 234 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.72-2.94 (m, 4H), 7.14-7.34 (m, 5H), 13.10 (s, 1H), 13.34 (s, 1H).

Example 20A

3-(5-Oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)propionic acid



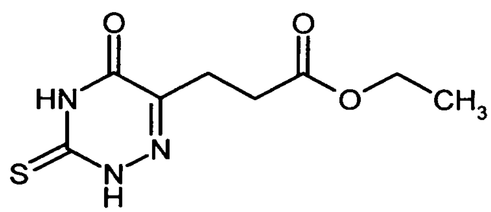
A solution of 2.25 g (24.69 mmol) of thiosemicarbazide and 4.99 g (24.69 mmol) of diethyl 2-oxoglutarate in 13 ml of ethanol is admixed with 123 µl of hydrochloric acid. After 18 h at room temperature the precipitated solid is filtered off, washed with ethanol and dried. The intermediate is taken up in 40 ml of ethanol/water 1/1, admixed with 2.77 g (49.38 mmol) of potassium hydroxide and stirred at reflux for 2 h. The pH is adjusted to 1 by means of hydrochloric acid. The solid formed is filtered off with suction and dried under a high vacuum. This gives 2.4 g (48% of theory) of the title compound.

HPLC (method 4): R_t = 1.29 min.

MS (EI): m/z = 202 $(M+H)^+$

Example 21A

Ethyl 3-(5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)propionate



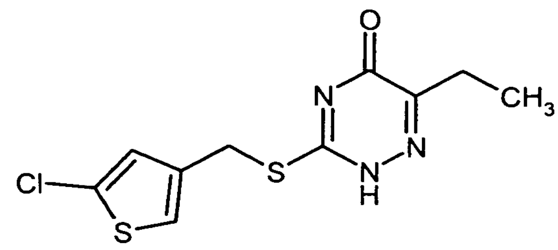
1.70 g (8.45 mmol) of 3-(5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)propionic acid are dissolved in 17 ml of ethanol, 740 µl (10.14 mmol) of thionyl chloride are added and the mixture is stirred at reflux overnight. The reaction mixture is concentrated and dried under a high vacuum. This gives 1.8 g (93% of theory) of the title compound.

LC-MS (method 3): R_t = 1.07 min.

MS (ESIpos): m/z = 230 $(M+H)^+$

Example 22A

3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one



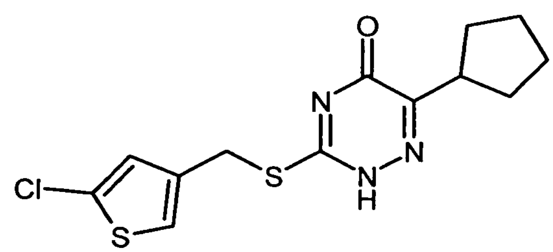
A solution of 200 mg (1.27 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 175.8 mg (1.27 mmol) of potassium carbonate in 15 ml of water is admixed with 214.7 mg (1.29 mmol) of 2-chloro-4-(chloromethyl)thiophene. After 14 h at room temperature heating is carried out at 80°C for 18 h. After the mixture has cooled the pH is adjusted to 1 using 2 N hydrochloric acid and the mixture is concentrated in vacuo to approximately 5 ml and purified by means of preparative HPLC. The product fractions are combined, concentrated in vacuo and dried under a high vacuum. This gives 155 mg (42% of theory) of the title compound.

HPLC (method 4): R_t = 4.02 min.

MS (EI): m/z = 288 $(M+H)^+$

Example 23A

3-{[(5-Chloro-3-thienyl)methyl]thio}-6-cyclopentyl-1,2,4-triazin-5(2H)-one



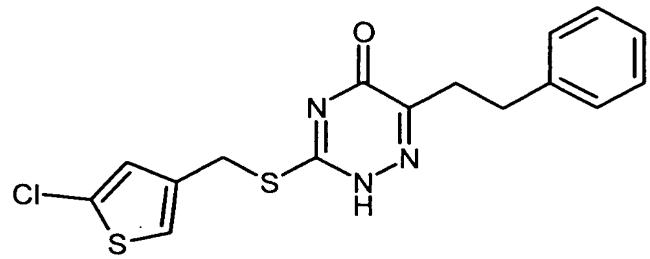
A solution of 300 mg (1.52 mmol) of 6-cyclopentyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one is admixed with 254 mg (1.52 mmol) of 2-chloro-4-(chloromethyl)thiophene and 397 µl (2.28 mmol) of *N,N*-diisopropylethylamine. After 2 h at room temperature the reaction mixture is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 202 mg (40% of theory) of the title compound.

LC-MS (method 5): R_t = 2.39 min.

MS (ESIpos): m/z = 328 $(M+H)^+$

Example 24A

3-{[(5-Chloro-3-thienyl)methyl]thio}-6-(2-phenylethyl)-1,2,4-triazin-5(2H)-one



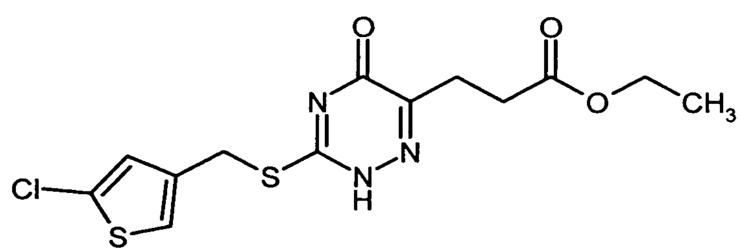
A solution of 300 mg (1.29 mmol) of 6-(2-phenylethyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one is admixed with 215 mg (1.29 mmol) of 2-chloro-4-(chloromethyl)thiophene and 340 µl (1.93 mmol) of *N,N*-diisopropylethylamine. After 2 h at room temperature the reaction mixture is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 174 mg (37% of theory) of the title compound.

LC-MS (method 3): R_t = 2.29 min.

MS (ESIpos): m/z = 364 $(M+H)^+$

Example 25A

Ethyl 3-(3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl)propionate



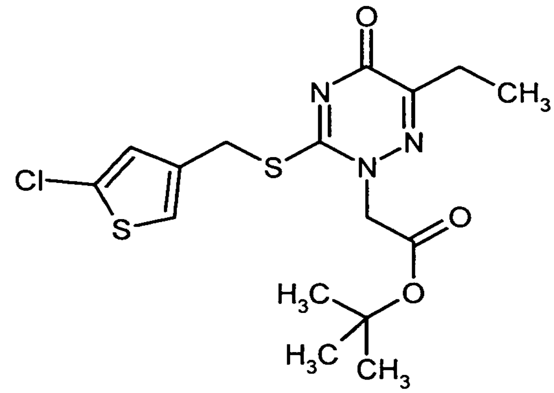
A solution of 300 mg (1.31 mmol) of ethyl 3-(5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)propionate is admixed with 219 mg (1.31 mmol) of 2-chloro-4-(chloromethyl)thiophene and 570 µl (3.27 mmol) of *N,N*-diisopropylethylamine. After 2 h at room temperature the reaction mixture is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 185 mg (39% of theory) of the title compound.

HPLC (method 4): R_t = 4.22 min.

MS (EI): m/z = 377 $(M+NH_4)^+$

Example 26A

tert-Butyl [3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



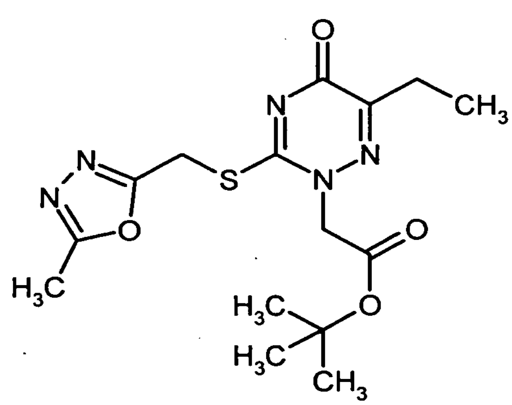
A solution of 500 mg (1.74 mmol) of 3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one in 7.2 ml of dichloromethane is admixed with 0.26 ml (1.74 mmol) of tert-butyl bromoacetate and 0.45 ml (2.61 mmol) of *N,N*-diisopropylethylamine. After 18 h at room temperature the reaction mixture is concentrated and the residue is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 495 mg (71% of theory) of the title compound.

HPLC (method 4): $R_t = 5.08$ min.

MS (EI): m/z = 402 $(M+H)^+$

Example 27A

tert-Butyl [6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



A solution of 150 mg (0.95 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one, 126.5 mg (0.95 mmol) of 2-(chloromethyl)-5-methyl-1,3,4-oxadiazole and 249.3 µl (1.43 mmol) of *N,N*-diisopropylethylamine is stirred at room temperature for 2 h. 140 µl (0.95 mmol) of tert-butyl

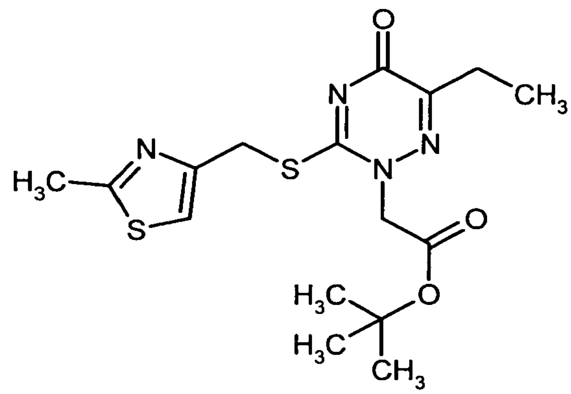
bromoacetate and a further 249.3 µl (1.43 mmol) of *N,N*-diisopropylethylamine are added. After 18 h at room temperature the contents of the flask are purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 105 mg (30% of theory) of the title compound.

HPLC (method 4): R_t = 4.10 min.

MS (EI): m/z = 368 $(M+H)^+$

Example 28A

tert-Butyl [6-ethyl-3-{[(2-methyl-1,3-thiazol-4-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



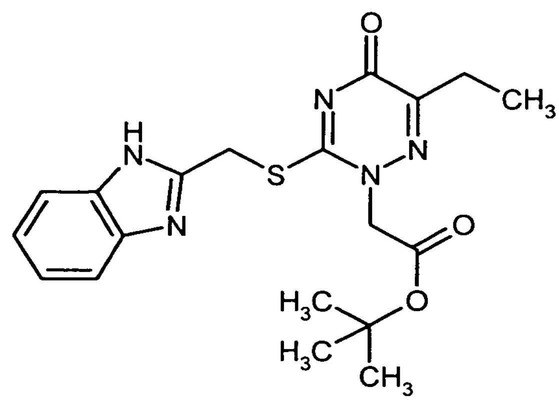
A solution of 200 mg (1.27 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one, 234.2 mg (1.27 mmol) of 4-(chloromethyl)-2-methyl-1,3-thiazole and 1.33 ml (7.63 mmol) of *N,N*-diisopropylethylamine is stirred at room temperature for 2 h. 187 µl (1.27 mmol) of tert-butyl bromoacetate are added. After 18 h at room temperature the contents of the flask are purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under high vacuum. This gives 140 mg (29% of theory) of the title compound.

LC-MS (method 5): R_t = 2.24 min.

MS (ESIpos): m/z = 383 $(M+H)^+$

Example 29A

tert-Butyl [3-[(1H-benzimidazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



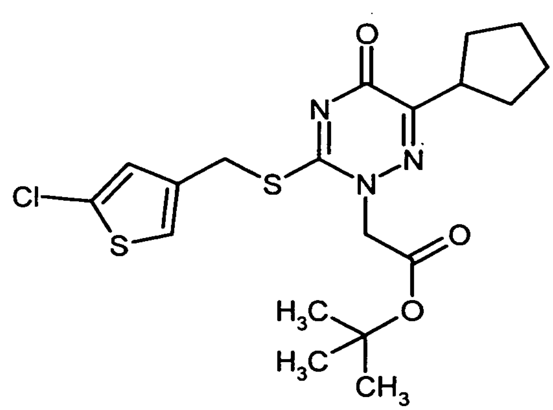
A solution of 200 mg (1.27 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one, 212 mg (1.27 mmol) of 2-(chloromethyl)-1H-benzimidazole and 665 µl (3.82 mmol) of *N,N*-diisopropylethylamine is stirred at room temperature for 2 h. 187 µl (1.27 mmol) of tert-butyl bromoacetate are added. After 18 h at room temperature the contents of the flask are purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 210 mg (41% of theory) of the title compound.

LC-MS (method 5): R_t = 1.83 min.

MS (ESIpos): m/z = 402 $(M+H)^+$

Example 30A

tert-Butyl 3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



A solution of 190 mg (0.58 mmol) of 3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-1,2,4-triazin-5(2H)-one in 3 ml of dichloromethane is admixed with 135.6 mg (0.70 mmol) of tert-butyl bromoacetate and 151.4 µl (0.87 mmol) of *N,N*-diisopropylethylamine. After 18 h at room

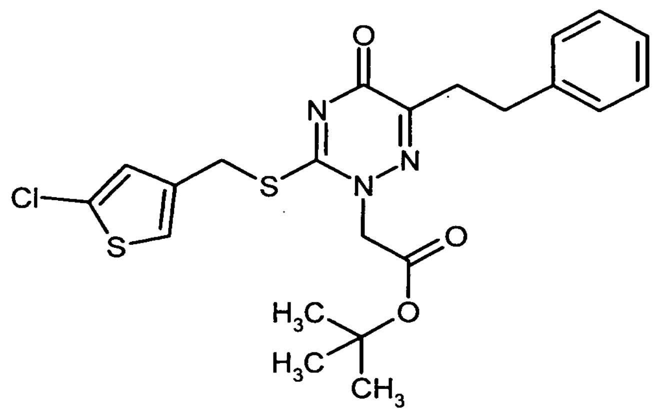
temperature the reaction mixture is concentrated and the residue is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 170 mg (66% of theory) of the title compound.

LC-MS (method 2): $R_t = 3.07$ min.

MS (ESIpos): m/z = 442 $(M+H)^+$

Example 31A

tert-Butyl [3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetate



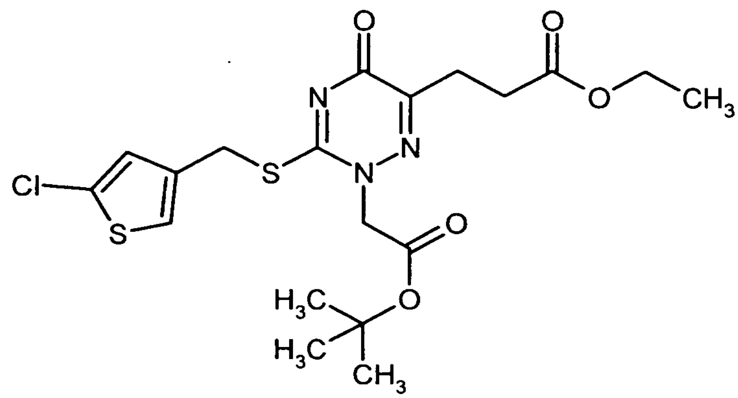
A solution of 174 mg (0.48 mmol) of 3-{[(5-chloro-3-thienyl)methyl]thio}-6-(2-phenylethyl)-1,2,4-triazin-5(2H)-one in 3 ml of dichloromethane is admixed with 74.1 µl (0.50 mmol) of tert-butyl bromoacetate and 124.9 µl (0.72 mmol) of *N,N*-diisopropylethylamine. After 18 h at room temperature the reaction mixture is concentrated and the residue is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 94 mg (41% of theory) of the title compound.

LC-MS (method 3): $R_t = 3.07$ min.

MS (ESIpos): m/z = 478 $(M+H)^+$

Example 32A

Ethyl 3-(2-(2-tert-butoxy-2-oxoethyl)-3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl)propionate



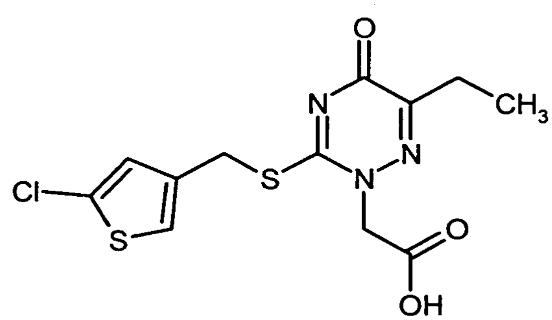
A solution of 90 mg (0.25 mmol) of ethyl 3-(3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl)propionate in 2 ml of dichloromethane is admixed with 51.2 mg (0.26 mmol) of tert-butyl bromoacetate and 70 µl (0.38 mmol) of *N,N*-diisopropylethylamine. After 18 h at room temperature the reaction mixture is concentrated and the residue is purified by means of preparative HPLC. The product fractions are combined, concentrated and dried under a high vacuum. This gives 90 mg (76% of theory) of the title compound.

HPLC (method 4): R_t = 5.04 min.

MS (EI): m/z = 474 $(M+H)^+$

Example 33A

[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



360 mg (0.90 mmol) of tert-butyl [3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate are reacted in a mixture of 8 ml of dichloromethane/TFA (1/1). After 18 h at room temperature the reaction mixture is concentrated and the concentrate is taken up in a little

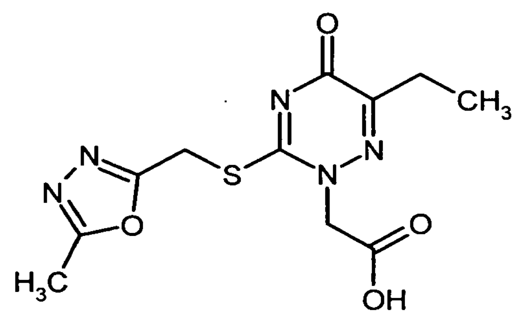
DMSO and purified by means of preparative HPLC. The product fractions are concentrated and dried under a high vacuum. This gives 225 mg (73% of theory) of the title compound.

HPLC (method 4): $R_t = 4.10$ min.

MS (EI): m/z = 346 $(M+H)^+$

Example 34A

[6-Ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



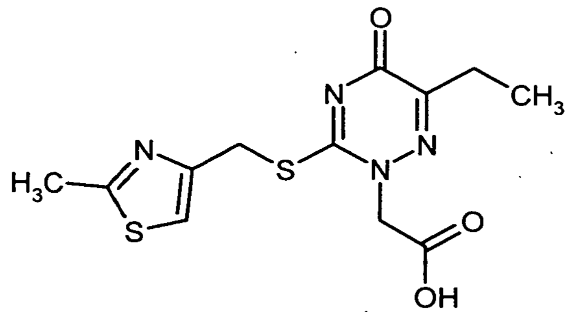
97 mg (0.26 mmol) of tert-butyl 6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetate are reacted in a mixture of 1.2 ml of dichloromethane/TFA (5/1). After 18 h at room temperature the reaction mixture is concentrated and the concentrate is taken up in a little DMSO and purified by means of preparative HPLC. The product fractions are combined and dried under a high vacuum. This gives 95 mg of a crude substance which is not purified further.

LC-MS (method 2): $R_t = 0.75$ min.

MS (ESIpos): m/z = 312 $(M+H)^+$

Example 35A

[6-Ethyl-3-{[(2-methyl-1,3-thiazol-4-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



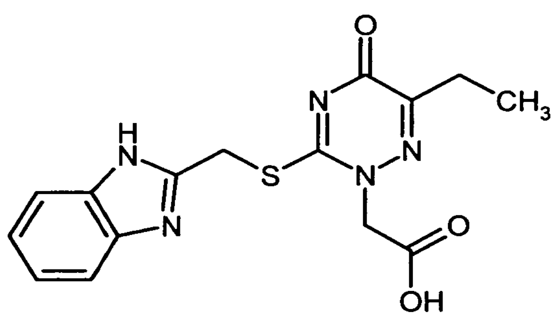
140 mg (0.37 mmol) of tert-butyl [6-ethyl-3-{[(2-methyl-1,3-thiazol-4-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetate are dissolved in 2 ml of dichloromethane. Following the addition of 282 µl (3.66 mmol) of TFA the mixture is stirred at room temperature for 18 h. It is taken up in acetonitrile/water, adjusted to a pH of 4-5 using 10% strength sodium hydrogencarbonate solution and purified by means of preparative HPLC. This gives 236 mg of a crude substance which is not purified further.

LC-MS (method 3): R_t = 1.09 min.

MS (ESIpos): m/z = 327 $(M+H)^+$

Example 36A

[3-[(1H-Benzimidazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



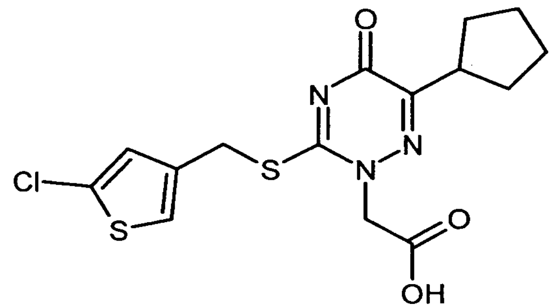
210 mg (0.52 mmol) of tert-butyl [3-[(1H-benzimidazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate are dissolved in 2 ml of dichloromethane. Following the addition of 403 µl (5.23 mmol) of TFA the reaction mixture is stirred at room temperature for 18 h.. It is taken up in acetonitrile/water, adjusted to a pH of 4-5 using 10% strength sodium hydrogencarbonate solution and purified by means of preparative HPLC. This gives 250 mg of a crude substance which is not purified further.

LC-MS (method 2): R_t = 1.21 min.

MS (ESIpos): m/z = 346 $(M+H)^+$

<u>**Example 37A**</u>

[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



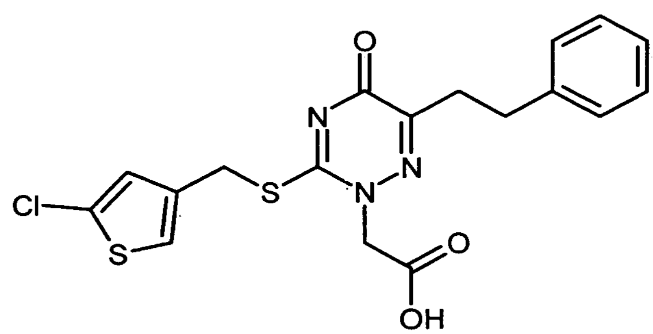
140 mg (0.31 mmol) of tert-butyl [3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate are reacted in a mixture of 2 ml of dichloromethane/TFA (3/1). After 18 h at room temperature the reaction mixture is concentrated and the concentrate is taken up in a little DMSO and purified by means of preparative HPLC. The product fractions are concentrated and dried under a high vacuum. This givens 125 mg of the title compound, which is not purified further.

LC-MS (method 3): R_t = 2.04 min.

MS (ESIpos): m/z = 386 $(M+H)^+$

<u>**Example 38A**</u>

[3-{[(5-Chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetic acid



94 mg (0.20 mmol) of tert-butyl [3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetate are reacted in a mixture of 4 ml of dichloromethane/TFA (1/1). After

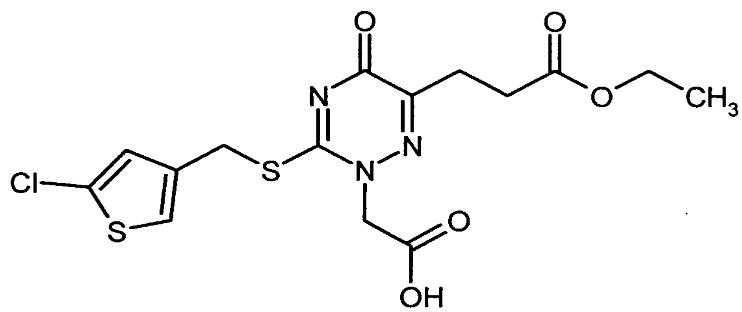
18 h at room temperature the reaction mixture is concentrated and the concentrate is taken up in a little DMSO and purified by means of preparative HPLC. The product fractions are concentrated and dried under a high vacuum. This gives 82 mg (99% of theory) of the title compound.

LC-MS (method 3): $R_t = 2.13$ min.

MS (ESIpos): m/z = 422 $(M+H)^+$

Example 39A

[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-(3-ethoxy-3-oxopropyl)-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



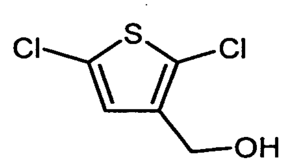
90 mg (0.19 mmol) of ethyl 3-(2-(2-tert-butoxy-2-oxoethyl)-3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl)propionate are reacted in a mixture of 3 ml of dichloromethane and 0.146 ml of TFA. After 18 h at room temperature the reaction mixture is concentrated and the concentrate is taken up in a little DMSO and purified by means of preparative HPLC. The product fractions are concentrated and dried under a high vacuum. This gives 90 mg of a crude substance which is not purified further.

HPLC (method 4): $R_t = 4.16$ min.

MS (EI): m/z = 418 $(M+H)^+$

Example 40A

(2,5-Dichloro-3-thienyl)methanol



13.9 ml (13.9 mmol) of a 1M solution of lithium aluminium hydride in THF is introduced as an initial charge under argon and at room temperature 5.0 g (23.2 mmol) of 2,5-dichlorothiophene-3-

carbonyl chloride in solution in 50 ml of THF are added dropwise. Stirring is continued for 30 minutes and then 1M hydrochloric acid is added dropwise to the reaction mixture until the precipitated solid redissolves. The solution is diluted with water and ethyl acetate and the organic phase is separated off and washed with water, dried over magnesium sulphate and concentrated in vacuo. This gives 3.58 g (84% of theory) of product.

TLC: R_f value: 0.29 (dichloromethane)

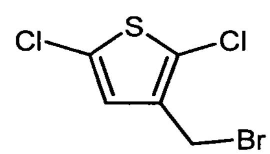
HPLC (method 6): R_t = 4.20 min.

MS (ESIpos): m/z = 182, 184 $(M)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.88 (s, 1H), 4.57 (s, 2H), 1.60 (s, broad, OH).

Example 41A

3-(Bromomethyl)-2,5-dichlorothiophene



A solution of 500 mg (2.73 mmol) of (2,5-dichloro-3-thienyl)methanol in 10 ml of dichloromethane is cooled to –5°C and slowly 0.1 ml (1.09 mmol) of phosphorus tribromide is added dropwise. The mixture is allowed to return to room temperature and is stirred for 15 minutes and the reaction is ended by adding water. The organic phase is separated off, dried over magnesium sulphate and concentrated in vacuo. This gives 570 mg (85% of theory) of product, which is reacted in the following step without further purification.

TLC: R_f value: 0.86 (dichloromethane)

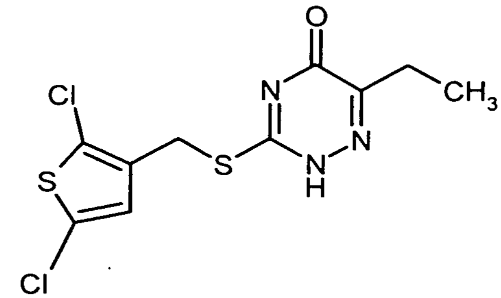
GC-MS (method 7): R_t= 6.52 min.

MS (CIpos): m/z = 246 $(M)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.83 (s, 1H), 4.35 (s, 2H).

Example 42A

3-{[(2,5-Dichloro-3-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one



A solution of 354 mg (2.25 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one and 312 mg (2.25 mmol) of potassium carbonate in 30 ml of water is admixed with 560 mg (2.28 mmol) of 3-(bromomethyl)-2,5-dichlorothiophene and stirred at room temperature overnight. The precipitated crystals are filtered off and washed repeatedly with water. The aqueous phase is extracted repeatedly with dichloromethane. The combined organic phases are dried over magnesium sulphate and concentrated in vacuo. The residue obtained is purified together with the precipitated crystals on silica gel (mobile phase: cyclohexane/ethyl acetate 3:1). This gives 270 mg (37% of theory) of product.

TLC: R_f value: 0.48 (cyclohexane/ethyl acetate 1:1)

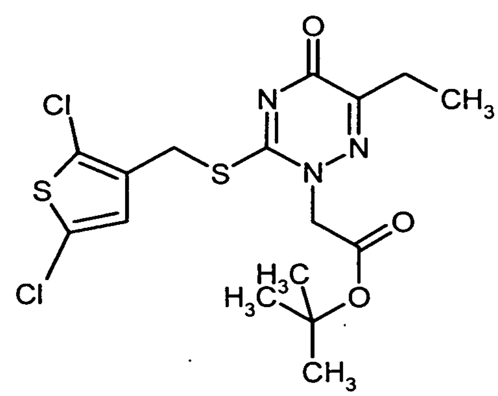
LC-MS (method 2): R_t= 2.25 min

MS (ESIpos): m/z = 322, 324 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.72 (s, broad, 1H), 6.88 (s, 1H), 4.37 (s, 2H), 2.72 (q, 2H), 1.21 (t, 3H).

Example 43A

tert-Butyl [3-{[(2,5-dichloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



A solution of 250 mg (0.78 mmol) of 3-{[(2,5-dichloro-3-thienyl)methyl]thio}-6-ethyl-1,2,4-triazin-5(2H)-one in 10 ml of dichloromethane is introduced as an initial charge under argon.

Subsequently 0.18 ml (1.0 mmol) of diisopropylethylamine and 0.14 ml (0.93 mmol) of tert-butyl bromoacetate are added and the mixture is stirred at 40°C overnight. The reaction solution is washed with water and the organic phase is separated off, dried over magnesium sulphate and concentrated in vacuo. The residue obtained is purified on silica gel (mobile phase: cyclohexane/ethyl acetate 3:1). This gives 163 mg (48% of theory) of product.

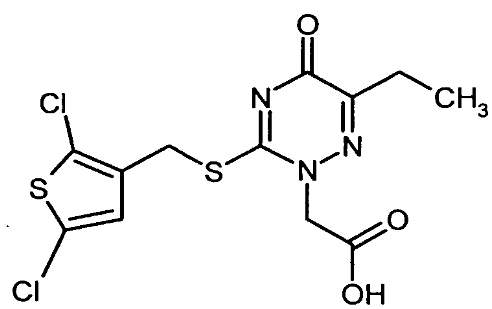
TLC: R_f value: 0.68 (cyclohexane/ethyl acetate 1:1)

MS (ESIpos): m/z = 436, 438 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.90 (s, 1H), 4.60 (s, 2H), 4.40 (s, 2H), 2.72 (q, 2H), 1.47 (s, 9H), 1.21 (t, 3H).

Example 44A

[3-{[(2,5-Dichloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



A solution of 140 mg (0.32 mmol) of tert-butyl-[3-{[(2,5-dichloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetate in 2 ml of dichloromethane is cooled to 0°C and 1 ml (13 mmol) of trifluoroacetic acid is slowly added dropwise. The mixture is stirred at room temperature overnight and the reaction is ended by adding water. The organic phase is washed with water, dried over magnesium sulphate and concentrated in vacuo. This gives 116 mg (95% of theory) of product, which is reacted in the following step without further purification.

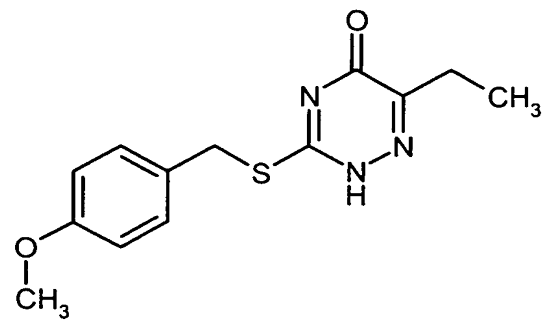
HPLC (method 6): R_t = 4.71 min.

LC-MS (method 2): R_t = 2.19 min.

MS (ESIpos): m/z = 380, 382 $(M+H)^+$

Example 45A

6-Ethyl-3-[(4-methoxybenzyl)thio]-1,2,4-triazin-5(2H)-one



A solution of 5.00 g (31.8 mmol) of 6-ethyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one and 4.39 g (31.8 mmol) of potassium carbonate in 250 ml water is admixed with 5.03 g (32.1 mmol) of 4-methoxybenzyl chloride and the mixture is stirred at room temperature overnight. The precipitated crystals are filtered off, washed with a little water and dried under a high vacuum at 40°C. This gives 5.56 g (63% of theory) of product. Following the addition of 1N hydrochloric acid it is possible to isolate a further 2.63 g (30% of theory) of product from the aqueous phase.

HPLC (method 6): R_t = 3.74 min.

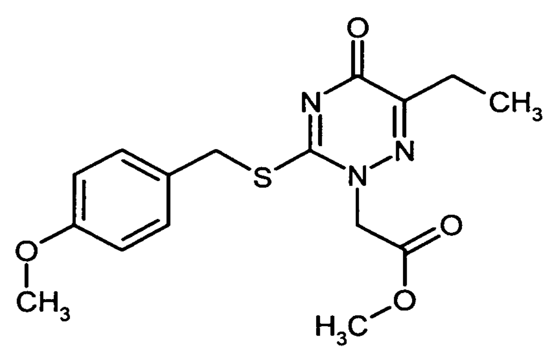
LC-MS (method 3): R_t = 1.81 min.

MS (ESIneg): m/z = 276 $(M-H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, 2H), 6.83 (d, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 2.70 (q, 2H), 1.19 (t, 3H).

Example 46A

Methyl [6-ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]acetate



A solution of 5.0 g (18 mmol) of 6-ethyl-3-[(4-methoxybenzyl)thio]-1,2,4-triazin-5(2H)-one in 170 ml of dichloromethane is introduced as an initial charge under argon. Subsequently 4.7 ml (27 mmol) of diisopropylethylamine and 2.05 ml (21.6 mmol) of methyl bromacetate are added and the mixture is stirred at room temperature overnight. Water is added to the reaction solution

and the organic phase is separated off. The organic phase is washed with water and pH 7 buffer, dried over magnesium sulphate and concentrated in vacuo. The residue obtained is purified on silica gel (mobile phase: dichloromethane/acetate 20:1). This gives 4.02 g (64% of theory) of product.

TLC: R_f value: 0.33 (dichloromethane/ethyl acetate 10:1)

HPLC (method 6): R_t = 4.17 min.

LC-MS (method 5): R_t = 2.22 min.

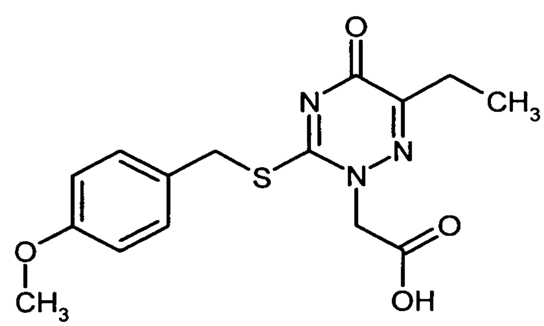
MS (ESIpos): m/z = 350 $(M+H)^+$

MS (DCI, NH_3): m/z = 350 $(M+H)^+$, 367 $(M+NH_4)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, 2H), 6.84 (d, 2H), 4.74 (s, 2H), 4.46 (s, 2H), 3.79 (s, 6H), 2.72 (q, 2H), 1.16 (t, 3H).

Example 47A

[6-Ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid



A solution of 4.00 g (11.5 mmol) of methyl [6-ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]acetate in 100 ml of dioxane is admixed with a 1M solution of 0.5 g (12.6 mmol) of sodium hydroxide in water and the mixture is stirred at room temperature for 5 h. The batch is acidified with 1N hydrochloric acid and extracted repeatedly with dichloromethane/ethyl acetate 1:1. The combined organic phases are dried over magnesium sulphate and concentrated in vacuo. This gives 3.04 g (79% of theory) of product.

HPLC (method 6): R_t= 3.86 min.

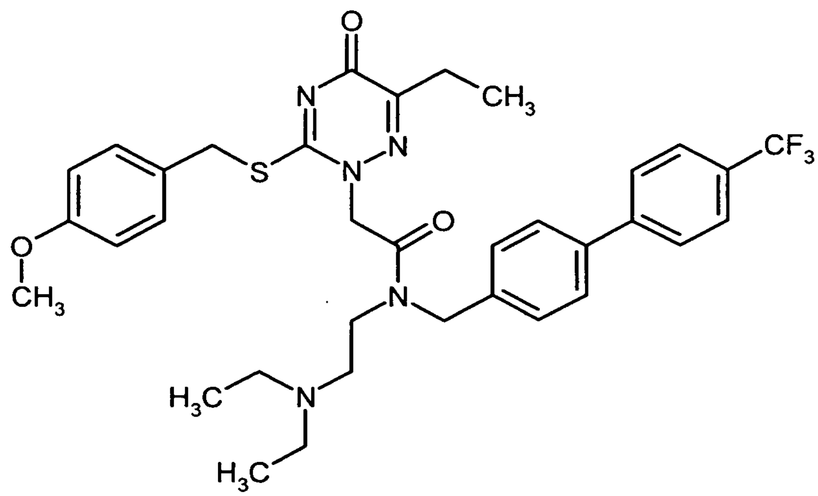
LC-MS (method 5): R_t= 1.70 min.

MS (ESIpos): m/z = 336 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.5 (s, broad, 1H), 7.35 (d, 2H), 6.88 (d, 2H), 4.80 (s, 2H), 4.40 (s, 2H), 3.74 (s, 3H), 2.56 (q, 2H), 1.12 (t, 3H).

Example 48A

N-[2-(Diethylamino)ethyl]-2-[6-ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



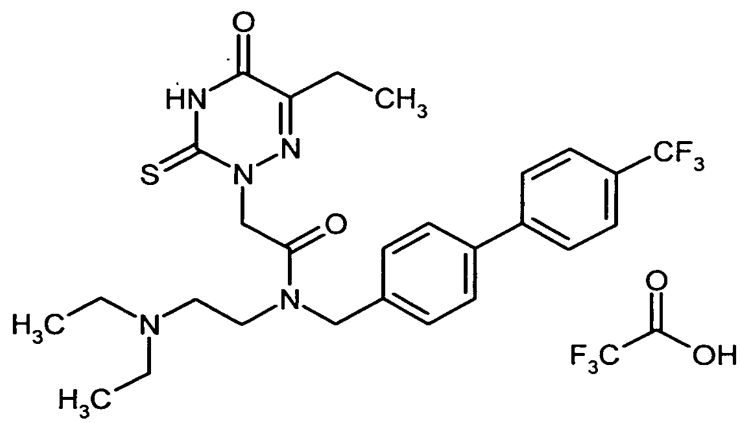
A solution of 3.0 g (8.95 mmol) of [6-ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid and 3.45 g (9.84 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]-methyl}ethane-1,2-diamine in 30 ml of DMF is admixed with 3.9 ml (22.4 mmol) of DIEA and 2.0 ml (11.6 mmol) of (benzotriazol-1-yloxy)bisdimethylaminomethylium fluoroborate and the batch is stirred at 40°C overnight. Following the addition of water the reaction mixture is extracted with dichloromethane. The combined organic phases are dried over magnesium sulphate and concentrated in vacuo. The residue obtained is purified on silica gel (mobile phase: dichloromethane/methanol 50:1). This gives 3.48 g (58% of theory) of product.

LC-MS (method 2): R_t= 2.22 min.

MS (ESIpos): m/z = 668 $(M+H)^+$

Example 49A

N-[2-(Diethylamino)ethyl]-2-(6-ethyl-5-oxo-3-thioxo-4,5-dihydro-1,2,4-triazin-2(3H)-yl)-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide trifluoroacetate



A solution of 3.4 g (5.1 mmol) of *N*-[2-(diethylamino)ethyl]-2-[6-ethyl-3-[(4-methoxybenzyl)thio]-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide in 150 ml of dichloromethane is admixed with 20 ml of trifluoroacetic acid and the batch is stirred at room temperature for 2 h. It is concentrated in vacuo and the residue is purified on silica gel (mobile phase: dichloromethane/methanol 100:1 to 40:1). This gives 2.5 g (75% of theory) of product.

HPLC (method 6): R_t = 3.33 min.

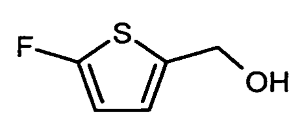
LC-MS (method 3): R_t = 2.13 min.

MS (ESIpos): m/z = 548 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.35 (s, broad, 1H), 9.50 (s, broad) and 9.20 (s, broad, together 1H), 7.95-7.72 (m, 6H), 7.54 (d) and 7.44 (d, together 2H), 5.37 (s) and 5.31 (s, together 2H), 4.77 (s) and 4.66 (s, together 2H), 3.73 (t) and 3.58 (t, together 2H), 3.23-3.10 (m, 6H), 2.56 (q, 2H), 1.22-1.06 (m, 9H).

Example 50A

(5-Fluoro-2-thienyl)methanol



1.8 ml (1.8 mmol) of a solution of lithium aluminium hydride in THF is introduced as an initial charge and 250 mg (1.7 mmol) of 5-fluorothiophene-2-carboxylic acid in 15 ml of THF are added

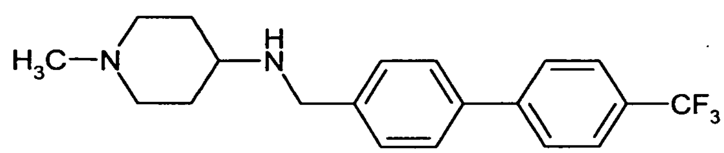
dropwise. The reaction mixture is stirred at room temperature for 1 h and 1M hydrochloric acid is added dropwise to it until the precipitated solid redissolves. The solution is extracted repeatedly with dichloromethane and the organic phase is dried over magnesium sulphate and concentrated in vacuo. This gives 204 mg (90% of theory) of product, which is reacted in the following step without further purification.

HPLC (method 6): R_t = 3.25 min.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.60 (t, 1H), 6.32 (dd, 1H), 4.68 (d, 2H), 1.70 (s, broad, 1H).

Example 51A

1-Methyl-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}piperidine-4-amine



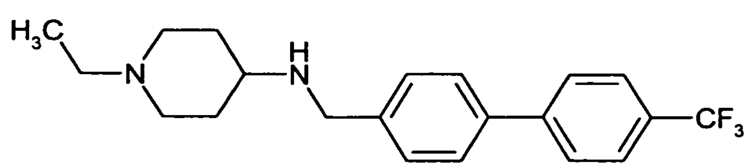
A solution of 1.5 g (5.97 mmol) of 1-[4'-(trifluoromethyl)biphenyl-4-yl]methanamine and 0.76 g (6.57 mmol) of 1-methyl-4-piperidone in a mixture of 15 ml of methanol and 1 ml of acetic acid is admixed with 0.45 g (7.16 mmol) of sodium cyanoborohydride. After 18 h at room temperature the reaction mixture is admixed with 30 ml 1N sodium hydroxide solution, the methanol is substantially stripped off on a rotary evaporator and the residue is extracted repeatedly with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated in vacuo. The crude material is dissolved in methanol and purified by preparative HPLC. This gives 1.64 g (78% of theory) of the title compound.

HPLC (method 4): R_t = 4.08 min.

MS (EI): m/z = 349 $(M+H)^+$.

Example 52A

1-Ethyl-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}piperidine-4-amine



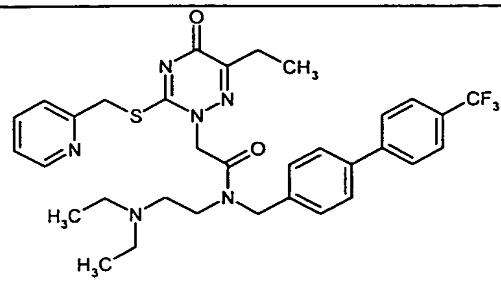
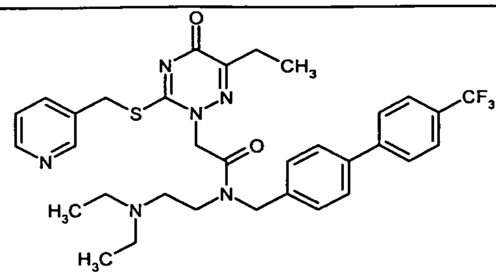
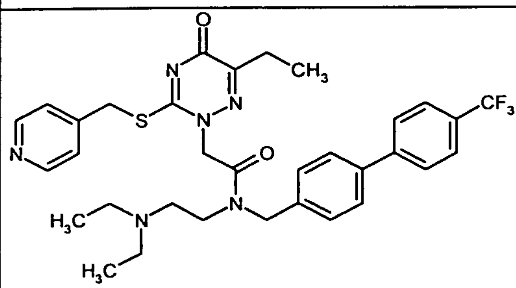
The preparation is analogous to that of Example 51A.

HPLC (method 4): $R_t = 4.19$ min.

MS (EI): m/z = 363 $(M+H)^+$.

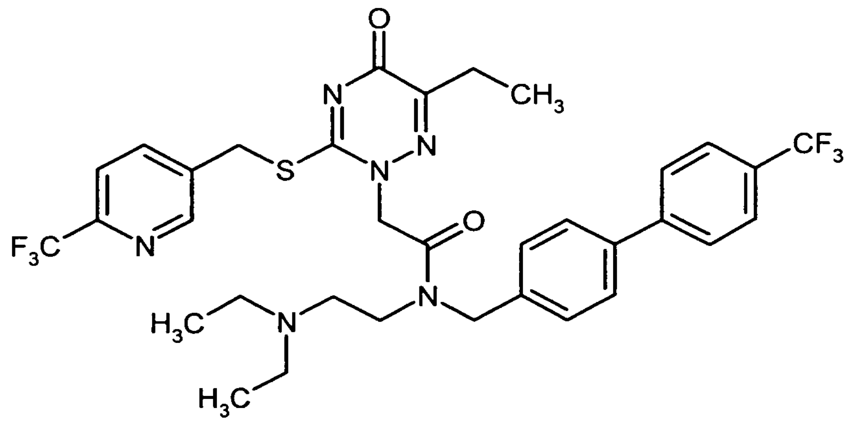
Working examples:

Examples 1 to 3 of the following table are prepared in the same way as for Example 4.

Example	Structure	Name
1		*N*-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-[(pyridin-2-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]-methyl}acetamide
2		*N*-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-[(pyridin-3-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]-methyl}acetamide
3		*N*-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-[(pyridin-4-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]-methyl}acetamide

Example 4

N-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



A solution of 19 mg (0.05 mmol) of [6-ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]-methyl}thio)-1,2,4-triazin-2(5H)-yl]acetic acid in 1 ml of dichloromethane is admixed with 21 mg (0.06 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 0.7 mg (0.01 mmol) of HOBt and 11 mg (0.06 mmol) of EDC. The reaction mixture is stirred for 18 h, admixed with 2 ml of water and concentrated in vacuo. The residue is purified by preparative HPLC. This gives 17 mg (48% of theory) of product.

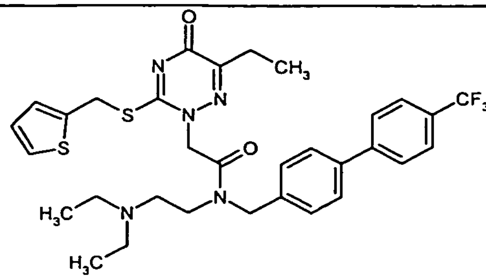
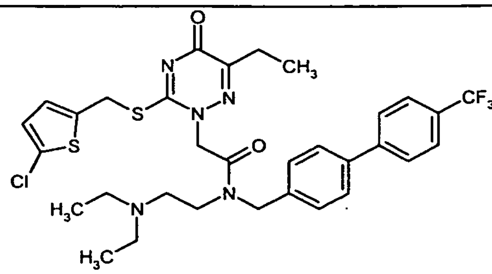
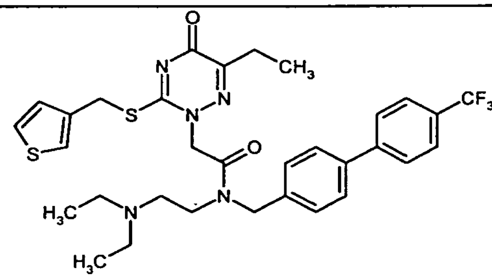
HPLC (method 6): R_t = 3.44 min.

LC-MS (method 3): R_t = 2.02 min.

MS (ESIpos): m/z = 707 $(M+H)^+$

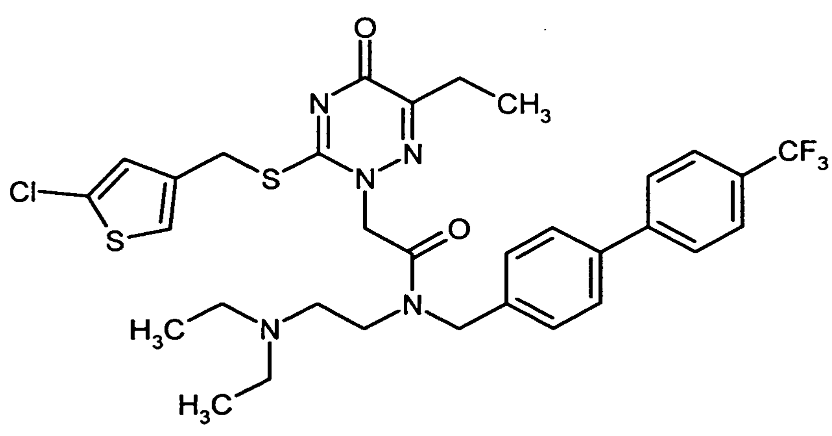
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.12 (s, 1H), 8.64 (d, 1H), 8.16 (d, 1H), 7.83 (dd, 6H), 7.56 (d, 2H), 5.45 (s, 2H), 4.97 (s, 2H), 4.79 (s, 2H), 4.19 (t, 2H), 3.54 (t, 2H), 3.43 (q, 4H), 2.77 (q, 2H), 1.38 (t, 6H), 1.22 (t, 3H).

Examples 5 to 7 of the table below are prepared in the same way as for Example 4.

Example	Structure	Name
5		*N*-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-[(2-thienylmethyl)thio]-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoro-methyl)biphenyl-4-yl]methyl}acetamide
6		2-[3-{[(5-Chloro-2-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-{[4'-(trifluoromethyl)-biphenyl-4-yl]methyl}acetamide
7		*N*-[2-(Diethylamino)ethyl]-2-[6-ethyl-5-oxo-3-[(3-thienylmethyl)thio]-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-acetamide

Example 8

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethyl-amino)ethyl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



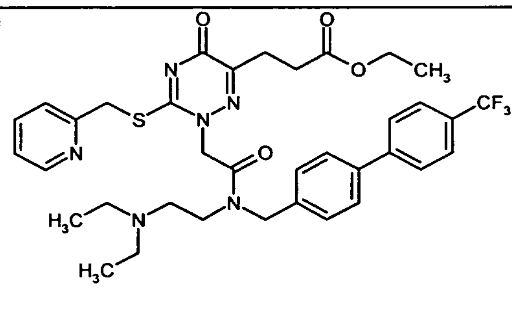
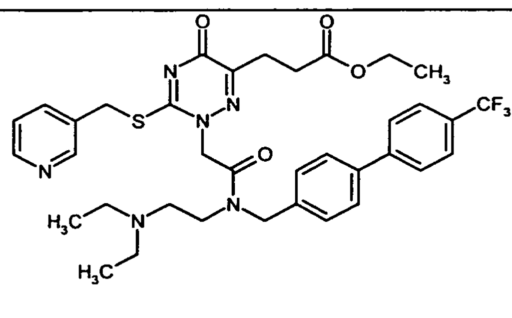
A solution of 140 mg (0.40 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid and 141.9 mg (0.40 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)-biphenyl-4-yl]methyl}ethane-1,2-diamine in 4 ml of dichloromethane is admixed at room temperature with 85.4 mg (0.45 mmol) of EDC and 5.5 mg (0.04 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 240 mg (87% of theory) of the title compound.

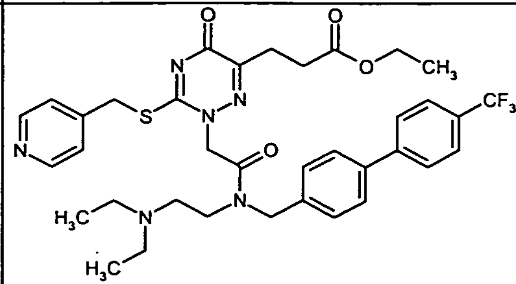
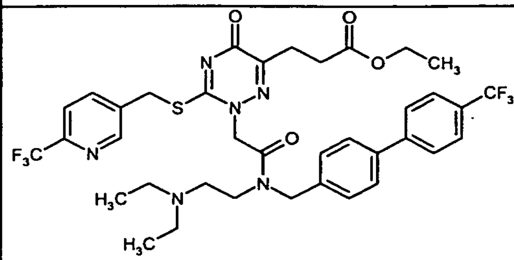
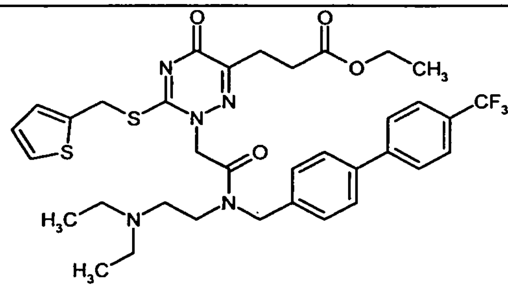
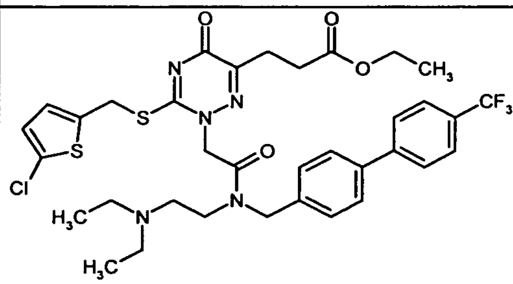
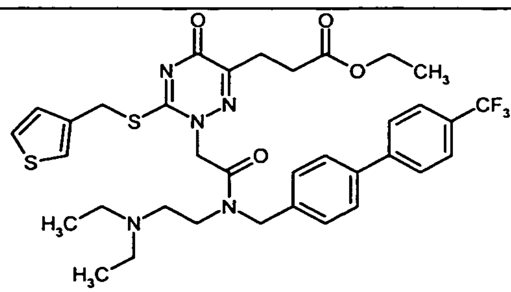
LC-MS (method 3): R_t = 2.49 min.

MS (ESIpos): m/z = 678 $(M+H)^+$

^{1}H-NMR (400 MHz, DCOOD): δ = 7.88-7.76 (m, 6H), 7.53 (m, 2H), 7.27 (m, 1H), 7.01 (m, 1H), 5.43 (s, 2H), 4.96 (s, 2H), 4.49 (s, 2H), 4.11 (m, 2H), 3.55 (m, 2H), 3.43 (q, 4H), 2.80 (q, 2H), 1.38 (tr, 6H), 1.25 (tr, 3H).

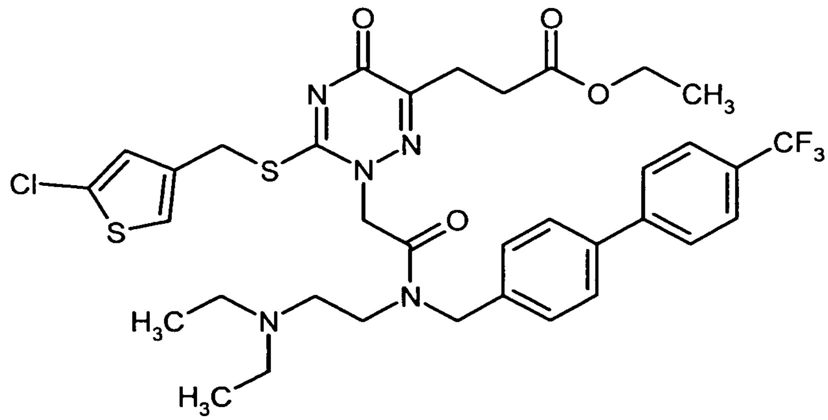
Examples 9 to 15 of the table below are prepared in the same way as for Example 4.

Example	Structure	Name
9		Ethyl 3-{2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-[(pyridin-2-ylmethyl)thio]-2,5-dihydro-1,2,4-triazin-6-yl}propionate
10		Ethyl 3-{2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-[(pyridin-3-ylmethyl)thio]-2,5-dihydro-1,2,4-triazin-6-yl}propionate

Example	Structure	Name
11		Ethyl 3-{2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-[(pyridin-4-ylmethyl)thio]-2,5-dihydro-1,2,4-triazin-6-yl}propionate
12		Ethyl 3-[2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-2,5-dihydro-1,2,4-triazin-6-yl]propionate
13		Ethyl 3-{2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-[(2-thienylmethyl)thio]-2,5-dihydro-1,2,4-triazin-6-yl}propionate
14		Ethyl 3-{3-{[(5-chloro-2-thienyl)methyl]thio}-2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl}propionate
15		Ethyl 3-{2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}-amino)-2-oxoethyl]-5-oxo-3-[(3-thienylmethyl)thio]-2,5-dihydro-1,2,4-triazin-6-yl}propionate

Example 16

Ethyl 3-{3-{[(5-chloro-3-thienyl)methyl]thio}-2-[2-([2-(diethylamino)ethyl]{[4'-(trifluoromethyl)-biphenyl-4-yl]methyl}amino)-2-oxoethyl]-5-oxo-2,5-dihydro-1,2,4-triazin-6-yl}propionate

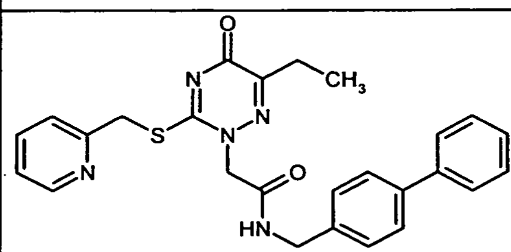


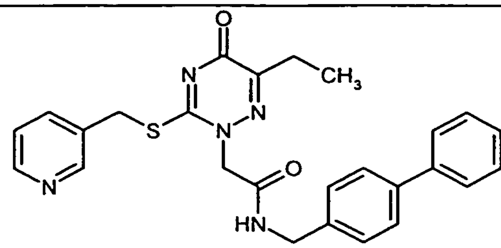
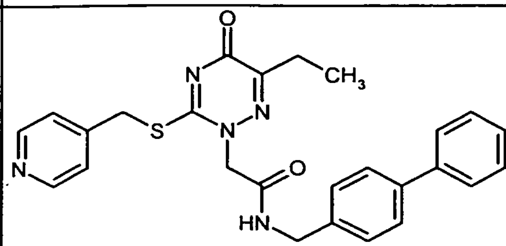
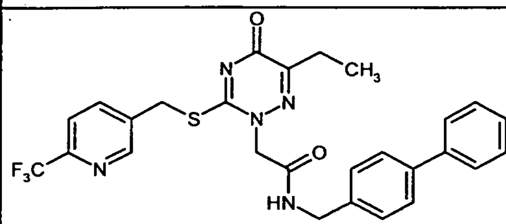
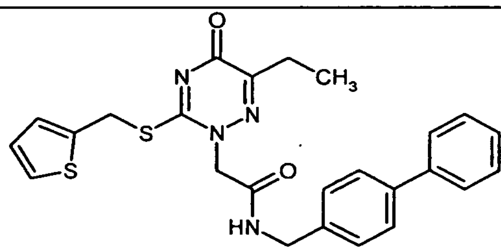
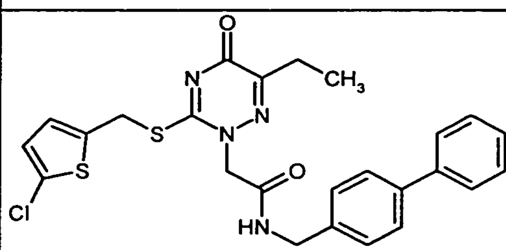
A solution of 90 mg (0.14 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-(3-ethoxy-3-oxopropyl)-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 49.8 mg (0.14 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 27.3 mg (0.10 mmol) of EDC and 1.9 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 23 mg (22% of theory) of the title compound.

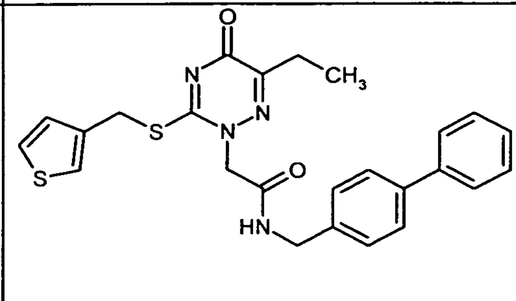
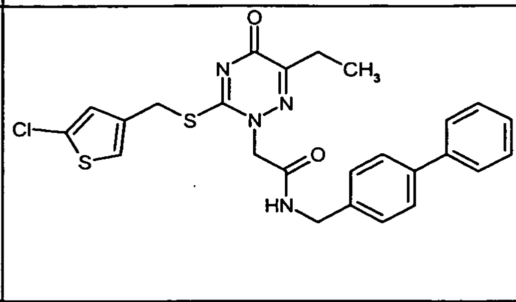
HPLC (method 4): R_t = 4.94 min.

MS (EI): m/z = 750 $(M+H)^+$

Examples 17 to 24 of the table below are prepared in the same way as for Example 4.

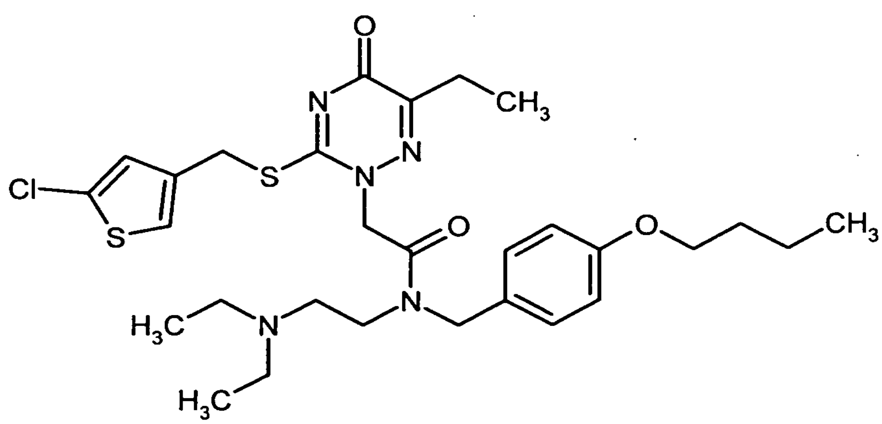
Ex-ample	Structure	Name
17		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-[(pyridin-2-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetamide

Ex-ample	Structure	Name
18		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-[(pyridin-3-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetamide
19		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-[(pyridin-4-ylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetamide
20		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}thio)-1,2,4-triazin-2(5H)-yl]acetamide
21		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-[(2-thienylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetamide
22		*N*-(Biphenyl-4-ylmethyl)-2-[3-{[(5-chloro-2-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetamide

Ex-ample	Structure	Name
23		*N*-(Biphenyl-4-ylmethyl)-2-[6-ethyl-5-oxo-3-[(3-thienylmethyl)thio]-1,2,4-triazin-2(5H)-yl]acetamide
24		*N*-(Biphenyl-4-ylmethyl)-2-[3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetamide

Example 25

N-(4-Butoxybenzyl)-2-[3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]acetamide



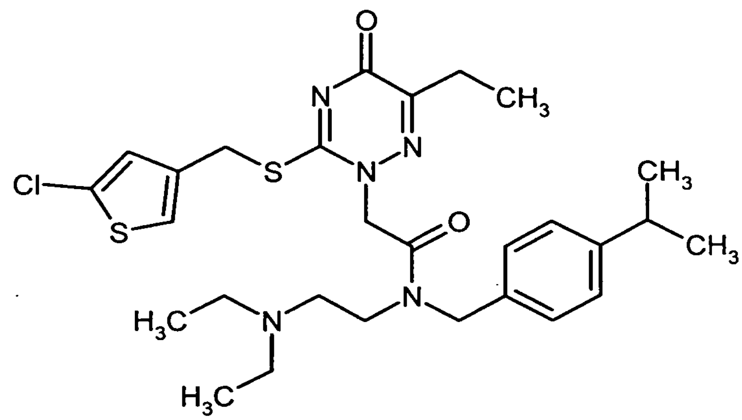
A solution of 85 mg (0.25 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 68.4 mg (0.25 mmol) of *N'*-(4-butoxybenzyl)-*N,N*-diethylethane-1,2-diamine, 47.1 mg (0.25 mmol) of EDC and 3.3 mg (0.02 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 27 mg (18% of theory) of the title compound.

LC-MS (method 2): R_t = 1.97 min.

MS (ESIpos): m/z = 606 $(M+H)^+$

Example 26

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-(4-isopropylbenzyl)acetamide



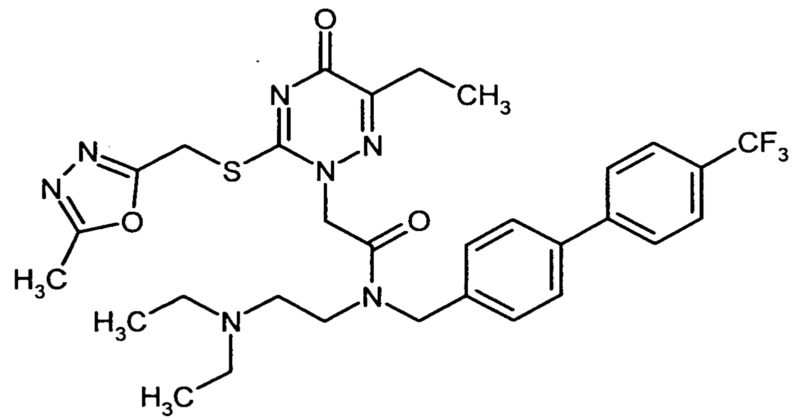
A solution of 85 mg (0.25 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 61.1 mg (0.25 mmol) of *N,N*-diethyl-*N'*-(4-isopropylbenzyl)ethane-1,2-diamine, 47.1 mg (0.25 mmol) of EDC and 3.3 mg (0.02 mmol) of HOBt. After 18 h at room temperature the reacton mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 41 mg (29% of theory) of the title compound.

LC-MS (method 3): R_t = 1.97 min.

MS (ESIpos): m/z = 576 $(M+H)^+$

Example 27

N-[2-(Diethylamino)ethyl]-2-[6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



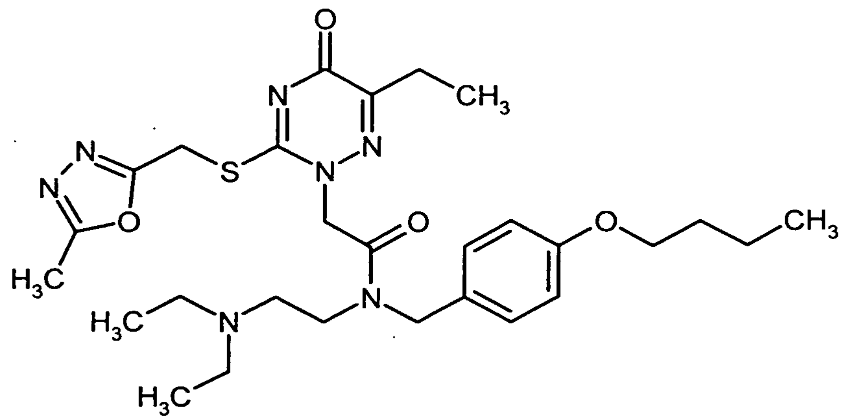
A solution of 40 mg (0.13 mmol) of [6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid and 45.0 mg (0.13 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine in 1 ml of DMF is admixed at room temperature with 27.1 mg (0.14 mmol) of EDC and 1.7 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 33 mg (40% of theory) of the title compound.

HPLC (method 4): R_t = 4.50 min.

MS (EI): m/z = 644 $(M+H)^+$

Example 28

N-(4-Butoxybenzyl)-*N*-[2-(diethylamino)ethyl]-2-[6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)-methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetamide



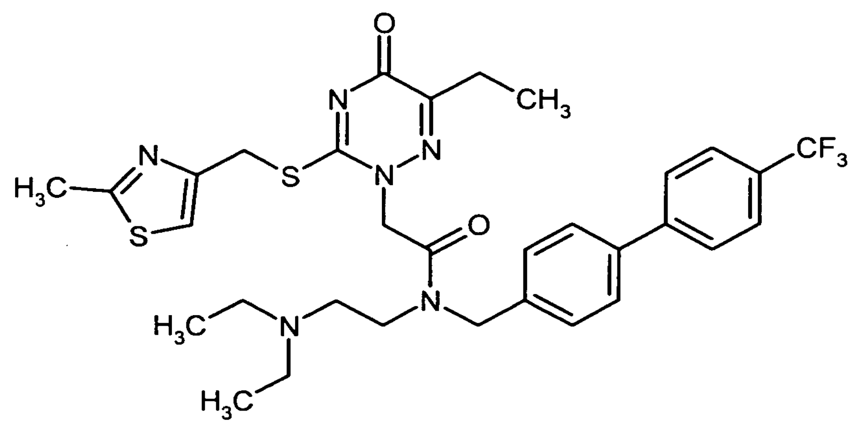
A solution of 54 mg (0.17 mmol) of [6-ethyl-3-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid and 48.3 mg (0.13 mmol) of *N'*-(4-butoxybenzyl)-*N,N*-diethylethane-1,2-diamine in 1 ml of DMF is admixed at room temperature with 36.6 mg (0.19 mmol) of EDC and 2.3 mg (0.02 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 43 mg (43% of theory) of the title compound.

HPLC (method 4): $R_t = 4.30$ min.

MS (EI): m/z = 572 $(M+H)^+$

Example 29

N-[2-(Diethylamino)ethyl]-2-[6-ethyl-3-{[(2-methyl-1,3-thiazol-4-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



A solution of 50 mg (0.15 mmol) of [6-ethyl-3-{[(2-methyl-1,3-thiazol-4-yl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of dichloromethane/DMF 1:1 is admixed with 53.7 mg (0.15 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 29.4 mg (0.15 mmol) of EDC and 2.1 mg (0.02 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 34 mg (34% of theory) of the title compound.

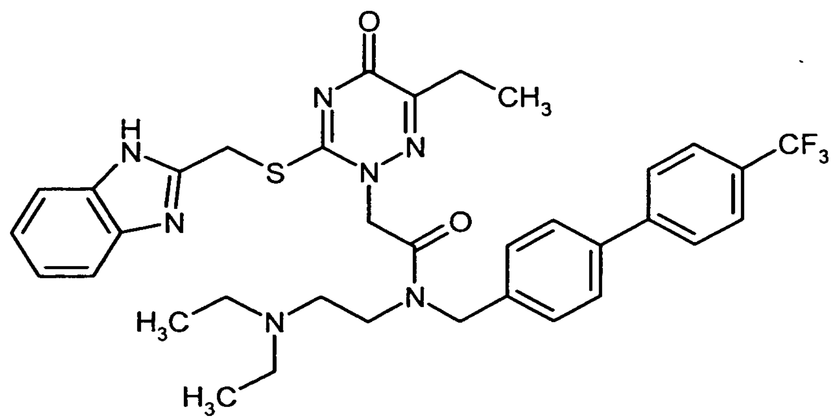
LC-MS (method 3): R_t = 1.97 min.

MS (ESIpos): m/z = 659 $(M+H)^+$

^{1}H-NMR (400 MHz, CF_3COOD): δ = 7.87 (s, 1H), 7.64 (m, 2H), 7.48 (m, 4H), 7.30 (m, 2H), 5.38 (s, 2H), 4.75 (s, 2H), 4.63 (s, 2H), 3.89 (m, 2H), 3.29 (m, 2H), 3.21 (q, 4H), 2.92 (s, 3H), 2.76 (q, 2H), 1.21 (tr, 6H), 1.18 (tr, 3H).

Example 30

2-[3-[(1H-Benzimidazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



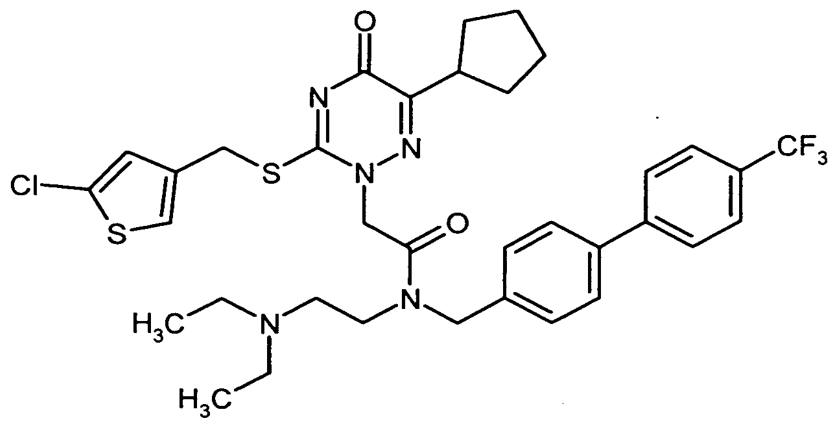
A solution of 50 mg (0.14 mmol) of [3-[(1H-benzimidazol-2-ylmethyl)thio]-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of dichloromethane/DMF 1:1 is admixed with 50.7 mg (0.14 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 27.8 mg (0.14 mmol) of EDC and 2.0 mg (0.01 mmol) or HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 28 mg (29% of theory) of the title compound.

LC-MS (method 3): R_t = 1.80 min.

MS (ESIpos): m/z = 678 $(M+H)^+$

Example 31

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



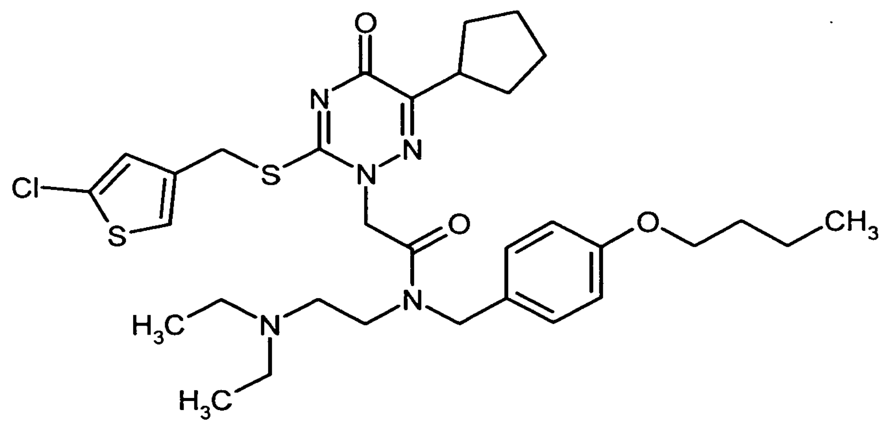
A solution of 42 mg (0.11 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 38.1 mg (0.11 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 20.9 mg (0.11 mmol) of EDC and 1.5 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high fraction give 29 mg (37% of theory) of the title compound.

LC-MS (method 3): $R_t = 2.40$ min.

MS (ESIpos): m/z = 718 $(M+H)^+$

Example 32

N-(4-Butoxybenzyl)-2-[3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]acetamide



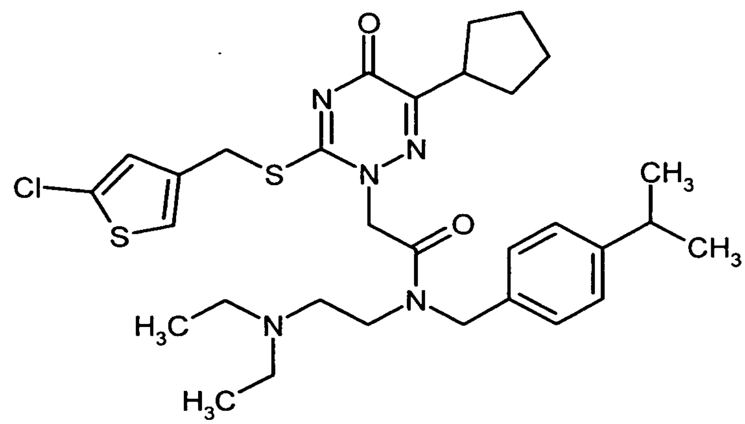
A solution of 42 mg (0.11 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 30.3 mg (0.11 mmol) of *N'*-(4-butoxybenzyl)-*N,N*-diethylethane-1,2-diamine, 20.9 mg (0.11 mmol) of EDC and 1.5 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 20 mg (28% of theory) of the title compound.

LC-MS (method 3): $R_t = 2.31$ min.

MS (ESIpos): m/z = 646 $(M+H)^+$

Example 33

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-(4-isopropylbenzyl)acetamide



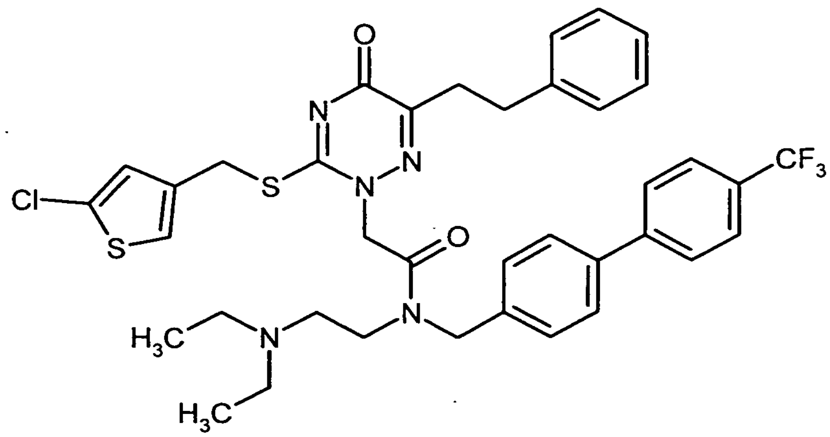
A solution of 42 mg (0.11 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-6-cyclopentyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 27.0 mg (0.11 mmol) of *N,N*-diethyl-*N'*-(4-isopropylbenzyl)ethane-1,2-diamine, 20.9 mg (0.11 mmol) of EDC and 1.5 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 9 mg (13% of theory) of the title compound.

LC-MS (method 3): R_t = 2.25 min.

MS (ESIpos): m/z = 616 $(M+H)^+$

Example 34

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



A solution of 41 mg (0.10 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 34.1 mg (0.10 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}ethane-1,2-diamine, 18.6 mg (0.10 mmol) of EDC and 1.3 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 44 mg (60% of theory) of the title compound.

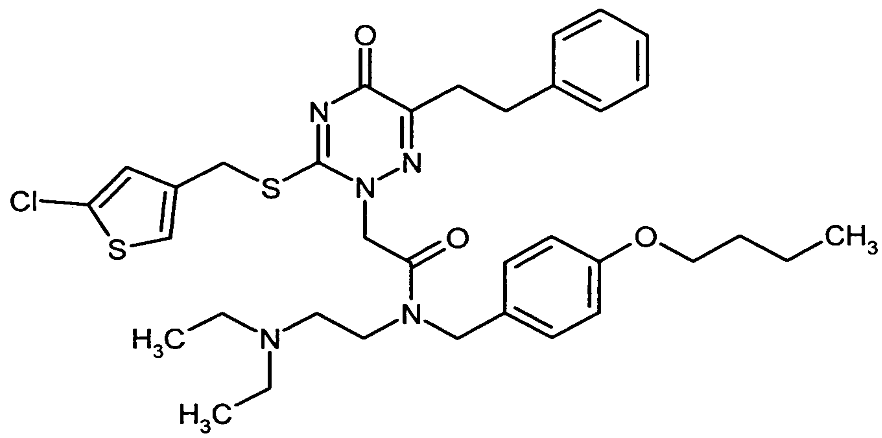
LC-MS (method 3): R_t = 2.39 min.

MS (ESIpos): m/z = 754 $(M+H)^+$

^{1}H-NMR (400 MHz, CF_3COOD): δ = 7.78 (m, 4H), 7.72 (m, 2H), 7.44 (m, 2H), 7.30 (m, 2H), 7.24 (m, 3H), 7.19 (s, 1H, partial H-D exchange), 6.89 (s, 1H), 5.50 (s, 2H), 4.91 (s, 2H), 4.60 (s, 2H), 4.11 (m, 2H), 3.55 (m, 2H), 3.41 (q, 4H), 3.30 (m, 2H), 3.15 (m, 2H), 1.42 (tr, 6H).

Example 35

N-(4-Butoxybenzyl)-2-[3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]acetamide



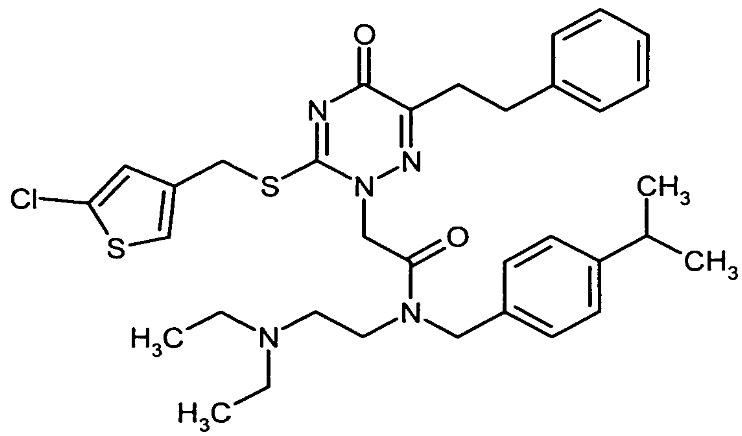
A solution of 41 mg (0.10 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 34.1 mg (0.10 mmol) of *N'*-(4-butoxybenzyl)-*N,N*-diethylethane-1,2-diamine, 18.6 mg (0.10 mmol) of EDC and 1.3 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 34 mg (51% of theory) of the title compound.

LC-MS (method 2): R_t = 2.16 min.

MS (ESIpos): m/z = 682 $(M+H)^+$

Example 36

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-(4-isopropylbenzyl)acetamide



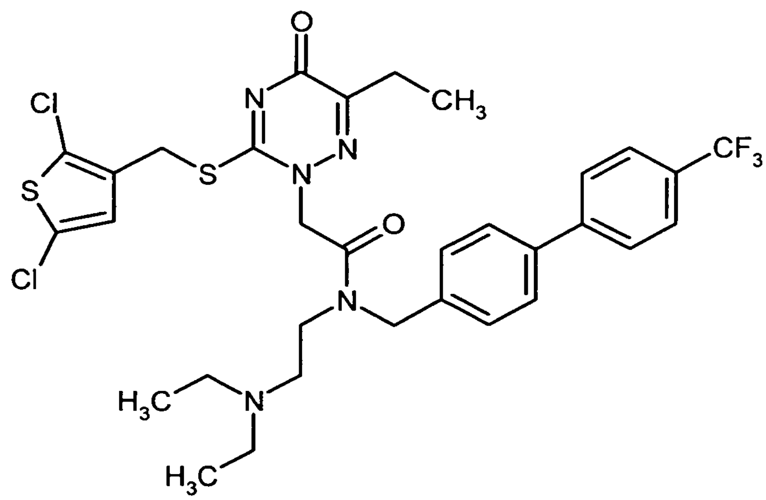
A solution of 35 mg (0.08 mmol) of [3-{[(5-chloro-3-thienyl)methyl]thio}-5-oxo-6-(2-phenylethyl)-1,2,4-triazin-2(5H)-yl]acetic acid in 2 ml of DMF is admixed with 20.6 mg (0.08 mmol) of *N,N*-diethyl-*N'*-(4-isopropylbenzyl)ethane-1,2-diamine, 15.9 mg (0.08 mmol) of EDC and 1.1 mg (0.01 mmol) of HOBt. After 18 h at room temperature the reaction mixture is purified by means of preparative HPLC. Concentration of the product fractions and drying under a high vacuum give 25 mg (46% of theory) of the title compound.

LC-MS (method 2): $R_t = 2.09$ min.

MS (ESIpos): m/z = 652 $(M+H)^+$

Example 37

2-[3-{[(2,5-Dichloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-[2-(diethylamino)ethyl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



A solution of 100 mg (0.26 mmol) of [3-{[(2,5-dichloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]acetic acid and 92 mg (0.26 mmol) of *N,N*-diethyl-*N'*-{[4'-(trifluoromethyl)-biphenyl-4-yl]methyl}ethane-1,2-diamine in dichloromethane is admixed with 4 mg (0.03 mmol) of HOBt and 55 mg (0.29 mmol) of EDC hydrochloride and the batch is stirred at room temperature overnight. Following the addition of water the organic phase is separated off, washed with saturated sodium hydrogencarbonate solution and water, dried over magnesium sulphate and concentrated in vacuo. The residue obtained is purified on silica gel (mobile phase: dichloromethane/methanol 40:1). This gives 66 mg (35% of theory) of product.

HPLC (method 6): R_t= 3.75 min.

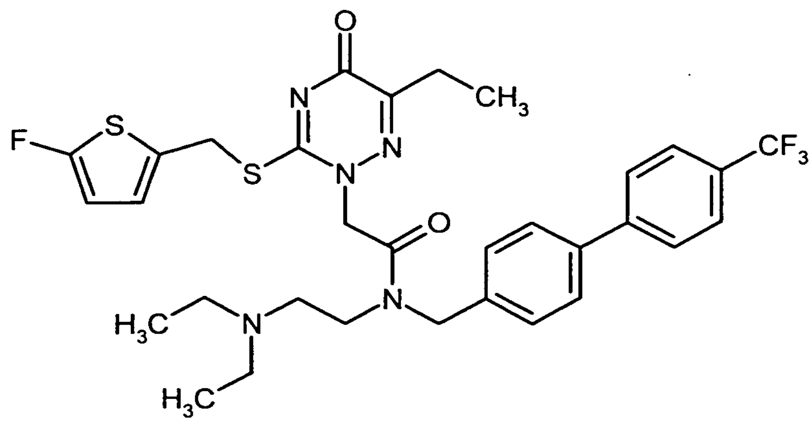
LC-MS (method 3): R_t = 2.39 min.

MS (ESIpos): m/z = 712, 714 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 - 7.58 (m, 4H), 7.61 (d) and 7.54 (d, together 2H), 7.35 (d, 2H), 6.93 (s) and 6.89 (s, together 1H), 5.17 (s) and 4.81 (s, together 2H), 4.70 (s, 2H), 4.43 (s) and 4.38 (s, together 2H), 3.55 (t) and 3.29 (t, together 2H), 2.78 -2.48 (m, 8H), 1.28 - 1.16 (m, 3H), 1.04 - 0.98 (m, 6H).

Example 38

N-[2-(Diethylamino)ethyl]-2-[6-ethyl-3-{[(5-fluoro-2-thienyl)methyl]thio}-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide



A solution, cooled at -10°C, of 50 mg (0.38 mmol) of (5-fluoro-2-thienyl)methanol in 1 ml of dichloromethane is admixed dropwise with 41 mg (0.15 mmol) of phosphorus tribromide and the batch is stirred at room temperature for 15 minutes. Water is added, the phases are separated and the organic phase is dried over magnesium sulphate and concentrated in vacuo. The residue is taken up in 1 ml of DMF, 80 mg (0.13 mmol) of *N*-[2-(diethylamino)ethyl]-2-(6-ethyl-5-oxo-3-thioxo-4,5-dihydro-1,2,4-triazin-2(3H)-yl)-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide trifluoroacetate and 64 mg (0.2 mmol) of caesium carbonate are added and the batch is stirred at room temperature overnight. Water is added to the reaction mixture which is extracted repeatedly with diethyl ether and the organic phase is dried over magnesium sulphate and concentrated in vacuo. The residue is purified by preparative HPLC. This gives 24 mg (27% of theory) of product.

HPLC (method 6): R_t = 3.53 min.

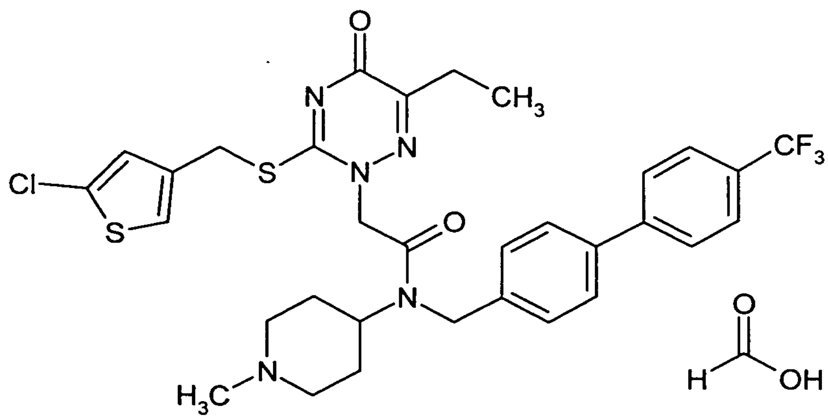
LC-MS (method 3): R_t= 2.18 min.

MS (ESIpos): m/z = 662 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.92-7.74 (m, 5H), 7.68 (d, 1H), 7.47-7.35 (m, 2H), 6.85-6.77 (m, 1H), 6.55-6.50 (m, 1H), 5.33 (s) and 5.02 (s, together 2H), 4.74 (s) and 4.63 (s, together 2H), 4.60-4.53 (m, 2H), 3.39-3.30 (m, 2H), 2.64-2.60 (m, 8H), 1.14-1-07 (m, 3H), 0.98-0.87 (m, 6H).

Example 39

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-(1-methylpiperidin-4-yl)-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamid, formate salt



The preparation starts from Example 33A and Example 51A, following the procedure of Example 4, using TBTU as coupling reagent. Purification by HPLC is carried out in the presence of formic acid in eluent A. The product is isolated as the formate salt.

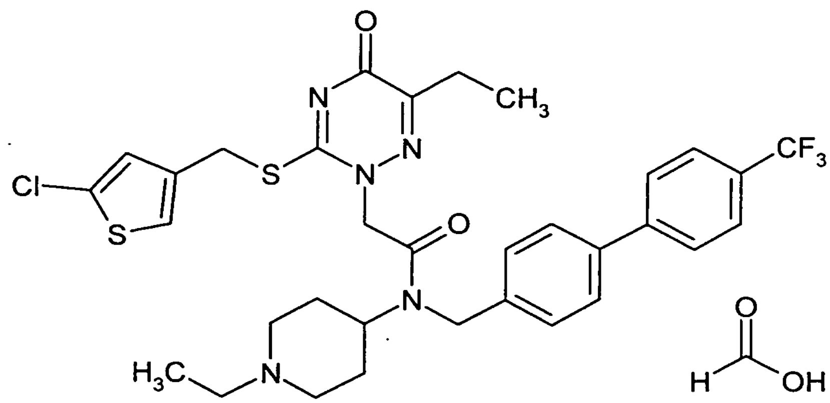
HPLC (method 4): R_t = 4.87 min.

MS (ESIpos): m/z = 676 (M+H)

^{1}H-NMR (400 MHz, TFA-d_1): δ = 8.2 (s, 1H), 7.8-6.8 (m, 10H), 5.4 (s, 2H), 4.9 (m, 3H), 4.6 (s, 2H), 3.8 (m, 2H), 3.3 (m, 2H), 3.1 (s, 3H), 3.0 (q, 2H), 2.5 (m, 2H), 2.3 (m, 2H), 1.4 (t, 3H). Rotamers of the amide compound occur; the signals described are those of the predominant rotamer.

Example 40

2-[3-{[(5-Chloro-3-thienyl)methyl]thio}-6-ethyl-5-oxo-1,2,4-triazin-2(5H)-yl]-*N*-(1-ethylpiperidin-4-yl)-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide, formate salt



The preparation starts from Example 33A and Example 52A, following the procedure of Example 4, using TBTU as coupling reagent. Purification by HPLC is carried out in the presence of formic acid in eluent A. The product is isolated as the formate salt.

HPLC (method 4): R_t = 4.90 min.

MS (ESIpos): m/z = 690 (M+H)

^{1}H-NMR (400 MHz, TFA-d_1): δ = 8.2 (s, 1H), 7.8-6.8 (m, 10H), 5.4 (s, 2H), 4.9 (m, 3H), 4.6 (s, 2H), 3.9 (m, 2H), 3.4 (m, 2H), 3.3 (m, 2H), 3.0 (q, 2H), 2.5 (m, 2H), 2.3 (m, 2H), 1.5 (t, 3H), 1.4 (t, 3H). Rotamers of the amide compound occur; the signals described are those of the predominant rotamer.

B) Evaluation of physiological activity

The suitability of the compounds of the invention for treating cardiovascular disorders can be demonstrated in the following assay systems:

In vitro assay of PAF-AH

Purification of PAF-AH from human plasma

PAF-AH activity is isolated from the LDL fraction of human plasma. This is done in accordance with a protocol of Stafforini et al. (*J. Biol. Chem.* **1987**, *262*: 4223-4230). Isolation of the LDL fraction by way of a potassium bromide density gradient is followed by solubilization with 0.1% of Tween 20 (buffer: 20 mM K_2HPO_4/KH_2PO_4, pH 6.8). This is followed by fractionation on a DEAE-Sepharose column (buffer: 20 mM K_2HPO_4/KH_2PO_4, pH 6.8, 0.1% Tween 20, gradient: 0-300 mM KCl). The fractions with PAF-AH activity are pooled, dialysed (50 mM Tris pH 7.5; 0.1% Tween 20) and then purified on a MonoQ column (buffer: 50 mM Tris pH 7.5; 0.1% Tween 20, gradient: 0-600 mM KCl).

Thio-PAF assay

2-Thio-PAF (Cayman Chemicals, Ann Arbor, MI, USA) is used as substrate for the PAF-AH. BODIPY FL L-cysteine (Molecular Probes, Eugene, OR, USA) serves as indicator for the free thiol group of the resultant product. The reaction is incubated in a buffer composed of 100 mM Tris-HCl, pH 8.2, 1 mM EGTA, 150 mM NaCl, 50 mM $MgCl_2$ with addition of 25 μM substrate, 10 μM indicator and 0.1 μg/ml PAF-AH at 37°C and the fluorescence (excitation 485 nm/ emission 515 nm) is measured in a Spectra Fluor fluorescence reader (Tecan, Crailsheim, Germany). The results are shown in Table A:

Table A:

Ex. No.	IC_{50} [nM]
6	60
31	15
34	20
35	100

Ex. No.	IC_{50} [nM]
38	40
39	5
40	4

In vivo assay of PAF-AH

The anti-atherosclerotic action of PAF-AH inhibitors is determined using the LDL receptor-deficient Watanabe rabbit (Buja, L.M., *Arteriosclerosis* **1983**, *3*, 87-101). Either the anti-atherosclerotic action is determined indirectly in accelerated studies (1-2 months) by altered gene expression of relevant marker genes in atherosclerosis-susceptible tissue, or the formation of atherosclerotic plaques is determined directly by means of histological techniques in long-term studies (3-6 months).

C) Working examples of pharmaceutical compositions

The substances of the invention can be converted as follows into pharmaceutical preparations:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch, 10 mg of polyvinylpyrrolidone (PVP 25) (BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 minutes. This mixture is compressed using a conventional tablet press (for tablet format see above).

Oral suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (FMC, USA) and 99 g of water.

10 ml oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol and the compound of Example 1 is added to the suspension. The water is added with stirring. The mixture is stirred for about 6 h until the swelling of the Rhodigel is at an end.

Solution for intravenous administration:

Composition:

1 mg of the compound of Example 1, 15 g of polyethylene glycol 400 and 250 g of water for injections.

Production:

The compound of Example 1 is dissolved together with polyethylene glycol 400 in the water with stirring. The solution is subjected to sterile filtration (pore diameter 0.22 μm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. The bottles are closed with infusion stoppers and crimp caps.